SYNTHESIS OF PHTHALIDES AND RELATED TOPICS AND THE ISOMERISATION OF A HOMOPHTHALIC ACID DERIVATIVE

W. R. ALLISON. JUNE 1959

T H E S I S

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by

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A C K N O W L E D G E M E N T S

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C O N T E N T S

P A R T I

Synthesis of Phthalides and Related Topics.

P A R T II

Isomerisation of a Homophthalic Acid Derivative.

PART I

Synthesis of Phthalides and Related Topics.

S U M M A R Y

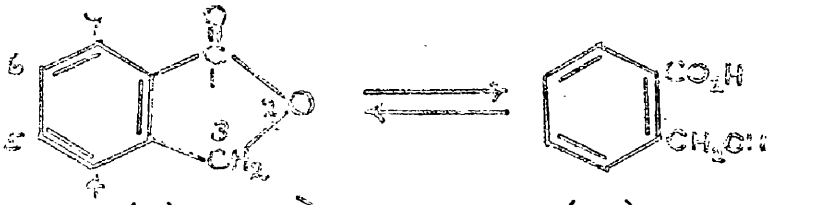
(a) The scope of the photobromination technique as a synthetic route to phthalide derivatives is discussed. The yields by this route have been improved by a new method for hydrolysis of orthobromomethyl esters to the corresponding bromophthalides. Thus ethyl dibromo-orsellinate has been converted into 5,7-dihydroxyphthalide, and ethyl everninate has been converted into 7-hydroxy-5-methoxyphthalide.

The relatively weak nature of the intramolecular hydrogen bond in 7-hydroxyphthalides has been further confirmed.

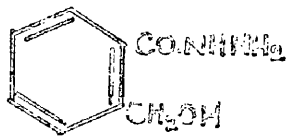
(b) A proposed synthesis of 7-methoxybenzo[1',2',5,6] phthalide using the above methods, required 1-hydroxy-3-methyl--2-naphthoic acid as starting material. On repeating the litorature method for preparation of the latter, a new compound was obtained, which has been identified as 2-carboxy-3-methyl--4-phenyl-3-butenoic acid. A mechanism has been proposed for its formation.

INTRODUCTION (a)

Phthalides have typical lactonic properties. Thus the lactone ring in phthalide (I) is opened by bases to give (II) and relactonisation occurs readily on acidification.

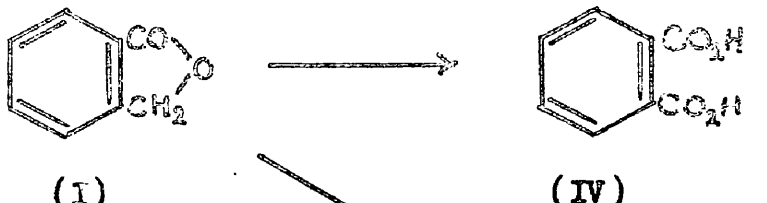


(I) (II)

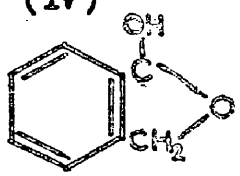


(III)

The phthalide ring is opened by certain reagents. For example phthalide (I) reacts with hydrazine[1] to give (III). Similar ring opening occurs on treatment with phenylhydrazine.[2] Phthalide (I) is oxidised to phthalic acid (IV) by potassium permanganate and is reduced by sodium amalgam to hydrophthalide (V).

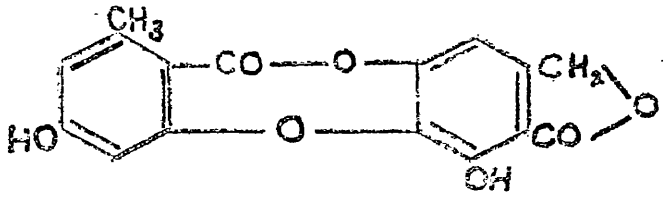


(I) (IV)



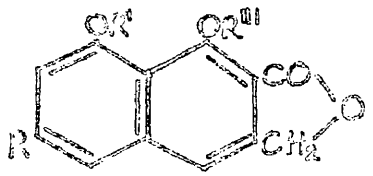
(V)

Phthalide derivatives do not occur frequently in nature, but a few have been isolated from plants and lichens. Variolaric acid (VI) has been isolated from the lichen Lecanora parella.[3] Two phthalides which have been formulated as



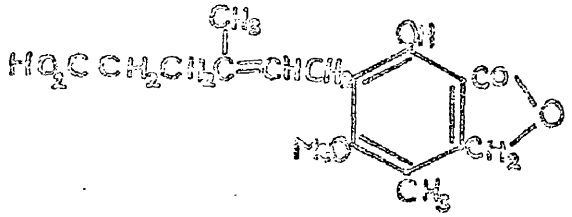
(VI)

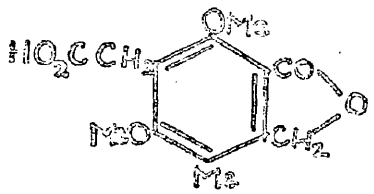
naphthalene derivatives were isolated from the bark of Rhamnus japonica.[4,5] They are α-sorigenin and β-sorigenin and their formulae are almost certainly (VII, R = OMe, R' = R'' = H)



(VII)

and (VII, R = R' = R'' = H) respectively.[6,7] Mycophenolic acid[8] (VIII) a metabolic product of strains of Penicillium brevi-compactum has antibacterial and antifungal properties.[9]

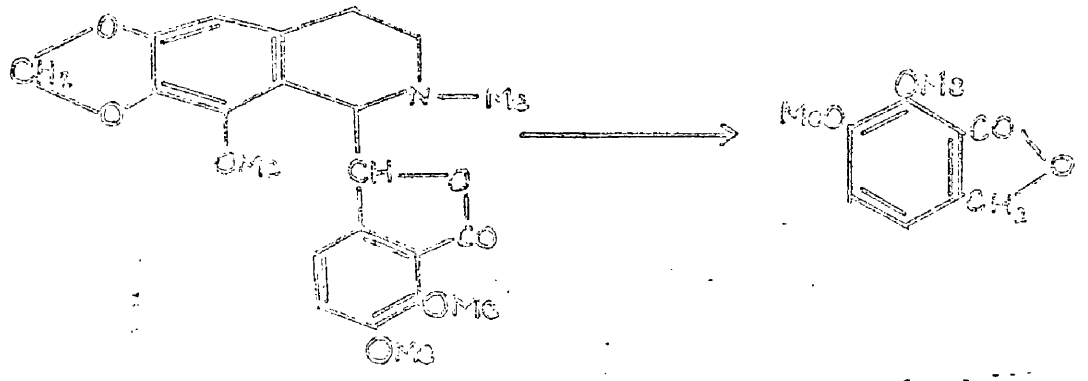




(VIII) (IX)

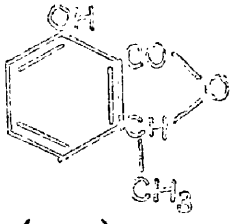
Phthalides occur as degradation products of naturally occurring compounds. Ozonolysis[10] of the methyl ether of mycophenolic acid (VIII) gives (IX). Narcotine[11] (X) which is itself a phthalide derivative on heating with zinc and

hydrochloric acid gives meconin (XI). Degradation products of



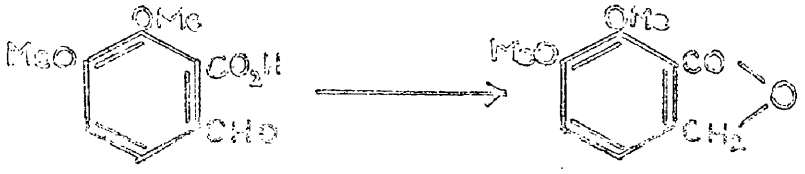
(X) (XI)

some lichen depsidones, possessing antibacterial activity, have been formulated as phthalide derivatives,[12] and 7-hydroxy-3-methylphthalide (XII) has been obtained by alkaline hydrolysis of terramycin.[13]



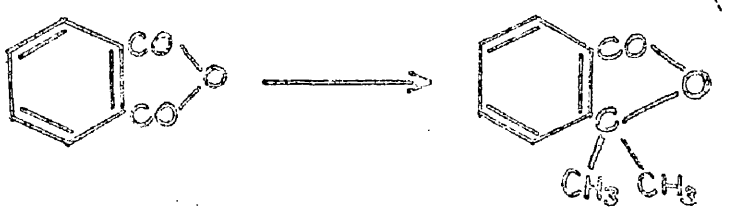
(XII)

A number of methods have been evolved for the synthesis of phthalides,[14] but these methods are not general. For example,



(XIII) (XI)

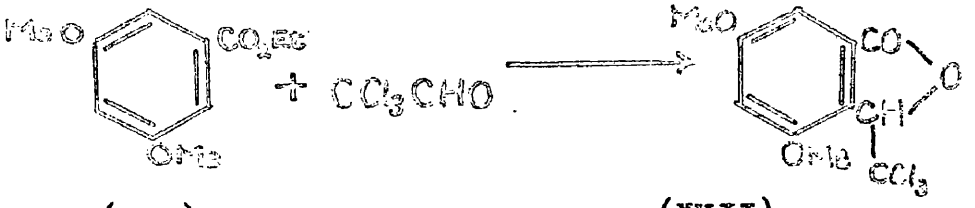
treatment of opianic acid (XIII) with sodium amalgam[18] gives meconin (XI), and treatment of phthalic anhydride (XIV) with



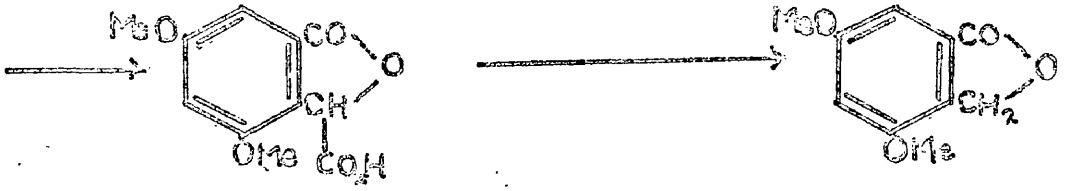
(XIV) (XV)

methyl magnesium iodide[16] gives 3-dimethylphthalide (XV).

A method of wider application was that of Fritsch,[17] an example of which is the following preparations of 4,6-dimethoxyphthalide (XIX). Ethyl 3,5-dimethoxybenzoate (XVI)



(XVI) (XVII)

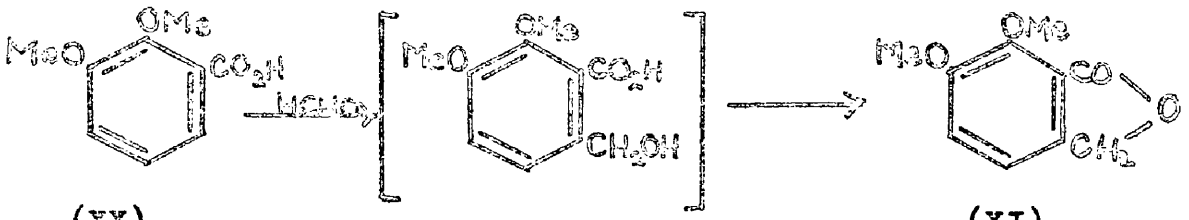


(XVIII) (XIX)

condensed with chloral in 90% sulphuric acid to give (XVII). Alkaline hydrolysis of (XVII) gave (XVIII) which was decarboxylated at 180° to (XIX).

A shorter route to substituted phthalides was that of Edwards, Perkin and Stoyle,[18] an example of which is the

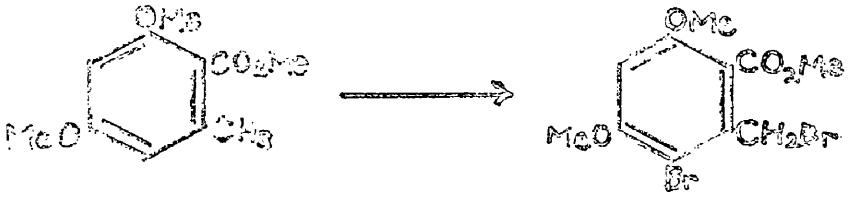
condensation of ortho-veratric acid (XX) with formaldehyde in



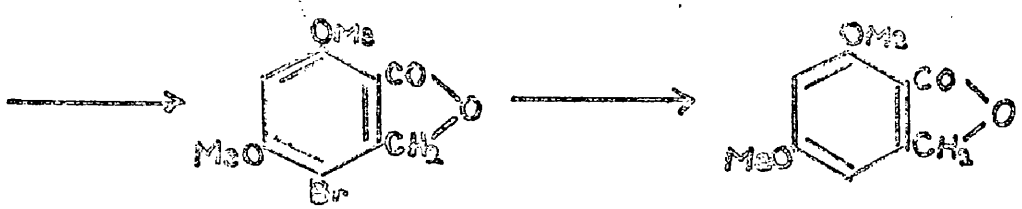
(XX) (XI)

concentrated hydrochloric acid to give meconin (XI). In some cases however, this reaction does not occur, and the carboxylic acid is returned unchanged. The scope and limitations of this method have been investigated by Charlesworth, Rennie, Sinder and Yan.[19]

The photobromination method described by Eliel et al.[20,21] showed some promise as a route towards substituted phthalides. Logan and Newbold[8] have used this method in the synthesis of 5,7-dimethoxyphthalide (XXIV) from methyl orsellinate dimethyl ether (XXI). Treatment of (XXI) with 2 mol. of bromine and



(XXI) (XXII)



(XXIII) (XXIV)

irradiation from a tungsten lamp gave methyl 3-bromo-2-bromomethyl--4,6-dimethoxybenzoate (XXII) which on alkaline hydrolysis gave

4-bromo-5,7-dimethoxyphthalide (XXIII). 5,7-Dimethoxyphthalide (XXIV) was obtained by catalytic hydrogenation of (XXIII).

Earlier methods for synthesising phthalides in this or similar ways are reported,[22-29] but in the earlier procedures, yields were stated to be poor[25] or were not given.[22-24] The reaction has attracted considerable interest from the theoretical point of view,[28] but its practical applications have been limited.[26,29-36]

The conditions employed by these earlier workers were not standard. In some cases sunlight was employed as the source of energy,[25,29,32] in others a mercury arc lamp,[32,35] and in others a tungsten lamp.[30,31,33,34] One method recommends anhydrous conditions,[30] and in another[35] water was deliberately added to dissolve the hydrogen bromide formed during the reaction. A small amount of iodine has been added as a catalyst in photobromination,[29,36] but Eliel et al.[20] found that iodine does not catalyse but inhibits the reaction, and in some cases completely prevents bromination from taking place. Most of the procedures are in agreement however with respect to the solvent, which has usually, been carbon tetrachloride or carbon disulphide, although in a few cases a solvent was not employed.[31,33]

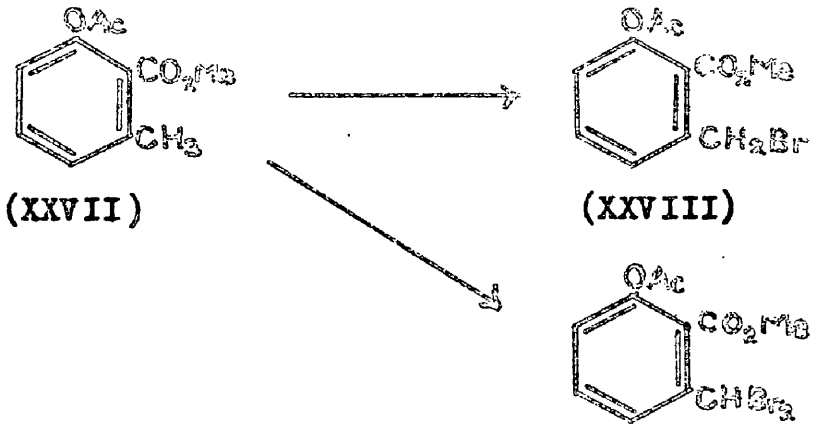
The positions at which bromine will most readily enter an aromatic molecule on photobromination are in doubt. Logan and Newbold[8] found that photobromination of orsellinic acid dimethyl ether (XXV) with 1½ mol. of bromine gave 3-bromo-4,6-dimethoxy-2-methylbenzoic acid (XXVI). Photobromination

of methyl orsellinate dimethyl ether (XXI) with 2 mol. of bromine gave methyl 3-bromo-2-bromomethyl-4,6-dimethoxybenzoate (XXII). On the basis of these results Logan and Newbold[3]

(XXV) (XXVI)

(XXI) (XXII)

suggest that bromination of the nucleus is required to activate the adjacent methyl group so that the subsequent side chain bromination can take place. On the other hand, Eliel et al.[21] found that methyl 2-acetoxy-6-methylbenzoate (XXVII) on photobromination with 1 mol. of bromine gave methyl 2-acetoxy--6-bromomethylbenzoate (XXVIII), while treatment with a further



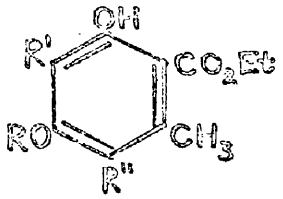
(XXVII) (XXVIII) (XXIX)

1 mol. of bromine gave methyl 2-acetoxy-6-dibromomethylbenzoate (XXIX).

THEORETICAL (a).

Interest has recently been shown in the preparation by various methods of substituted phthalides and phthaldehydic acids.[8,37,38,39] In connection with the structural elucidation of mycophenolic acid (VIII) Logan and Newbold[8] used the photobromination technique of Eliel *et al.*[20,21] to prepare 5,7-dimethoxyphthalide (XXIV) from methyl orsellinate dimethyl ether (XXI). [See 'Introduction'].

The photobromination technique has so far been applied to a few compounds only.[8,20,21] Our aim in this work was to examine the products of photobromination of orcinol derivatives



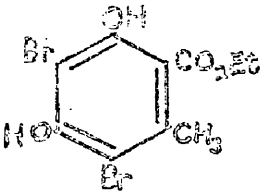
R = H or Me
R' = H or Br
R'' = H or Br

(XXX)

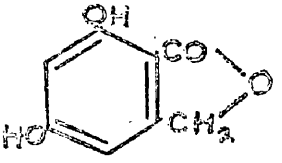
of the type (XXX), to determine the conditions of hydrolysis required to convert orthobromomethyl esters thus obtained to the corresponding phthalides, and thus to investigate the scope of the photobromination technique as a route to substituted phthalides.

Two series of experiments were carried out. In the first, photobromination of ethyl 3,5-dibromo-4,6-dihydroxy-2-methylbenzoate (XXXIV) was investigated as the first step in a possible synthesis of 5,7-dihydroxyphthalide (XXXI). In the

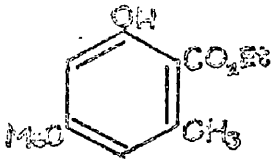
second series, the photobromination products of ethyl everninate (XLIII) were investigated as a possible route to 7-hydroxy-5--methoxyphthalide (XXXII). It was desired to examine the infrared spectra of (XXXI) and (XXXII) and of phthalides intermediate in their syntheses to determine whether they agreed with



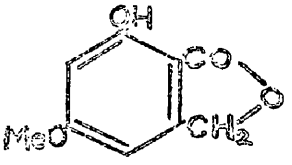
(XXXIV)



(XXXI)



(XLIII)



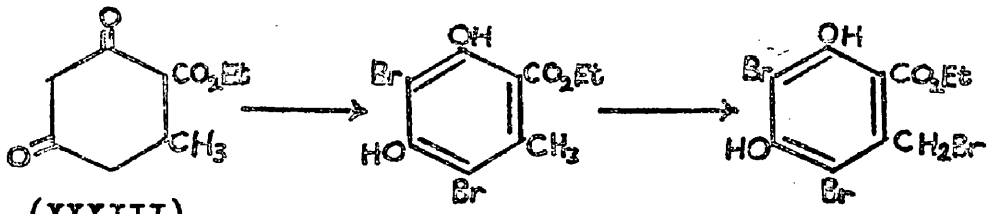
(XXXII)

the findings Duncanson, Grove and Zealley[40] concerning the carbonyl stretching frequencies of 7-hydroxyphthalides.

The synthesis of the phthalides (XXXI) and (XXXII) was also of interest since 5,7-dihydroxyphthalide (XXXI) could be postulated as a possible intermediate, along with orsellinic acid in the biosynthesis of variolaric acid[8] (VI), and 5-methoxy--7-hydroxyphthalide (XXXII) might serve as an intermediate in the synthesis of mycophenolic acid[8] (VIII).

Synthesis of 5,7-Dihydroxyphthalide (XXXI).

Ethyl 3,5-dibromo-4,6-dihydroxy-2-methylbenzoate (XXXIV) was prepared after the method of Sonn,[59] by aromatisation of 6-ethoxycarbonyl-5-methyl-1,3-dioxocyclohexane (XXXIII) with bromine in acetic acid. On photobromination (XXXIV) readily took up 1 mol. of bromine to give ethyl 3,5-dibromo-2-bromomethyl-4,6-



dihydroxybenzoate (XXXV) in good yield. The photobromination, and all others in this work were carried out as described by Eliel et al.[20,21] A solution of the material in dry carbon tetrachloride in a quartz flask, was refluxed gently by the irradiation from a 150 w. tungsten filament lamp. A solution of bromine in dry carbon tetrachloride was added dropwise to the refluxing solution. Each addition was made only after the colour of the previous addition had almost disappeared.

On attempted hydrolysis of (XXXV) with aqueous sodium hydroxide the solution darkened immediately and no product could be isolated. On hydrolysis of (XXXV) with aqueous sodium carbonate the solution again darkened rapidly, but 4,6-dibromo--5,7-dihydroxyphthalide (XXXVI) was isolated in very low yield (5-10%). The phthalide (XXXVI) gave a diacetate 5,7-diacetoxy-

-4,6-dibromophthalide (XXXVII) and a dimethyl ether 4,6-dibromo--5,7-dimethoxyphthalide (XXXVIII).

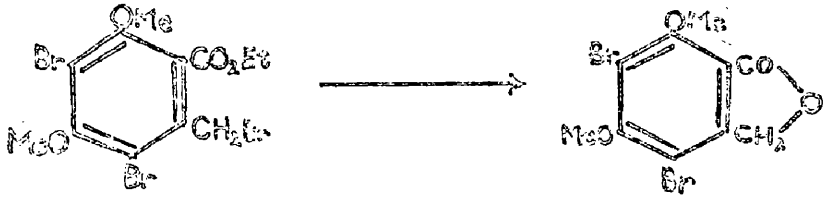
(XXXV) (XXXVI)

(XXXVII) (XXXVIII)

In view of the poor yield of (XXXVI), the hydrolysis was repeated in an atmosphere of nitrogen, but similar decomposition was observed. When (XXXV) was refluxed for a few hours with aqueous methanol however, a 20% yield of the phthalide (XXXVI) was obtained. Similar treatment of (XXXV) with aqueous ethanol gave a 50% yield of (XXXVI). Assuming that the yield of the phthalide (XXXVI) from this reaction varies with the b.p. of the aqueous solvent, we refluxed a solution of (XXXV) in aqueous dioxan. The yields of (XXXVI) thus obtained were in the range 85-95%. Due to hydrogen bromide liberated during the reaction, the hydrolysis is taking place under mildly acidic conditions. When, however, the acid concentration was raised by addition of dilute hydrochloric acid to the aqueous dioxan hydrolysis of

ethyl 3,5-dibromo-2-bromomethyl-4,6-dihydroxybenzoate (XXXV), the yield of the phthalide dropped to 16%.

The action of aqueous dioxan on another ortho-bromomethyl ester was examined. Methylation of ethyl 3,5-dibromo-2-bromomethyl-4,6-dihydroxybenzoate (XXXV) gave ethyl 3,5-dibromo-2--bromomethyl-4,6-dimethoxybenzoate (XXXIX) as an uncrystallisable oil. On refluxing (XXXIX) with aqueous dioxan, an 85% yield of



(XXXIX) (XXXVIII)

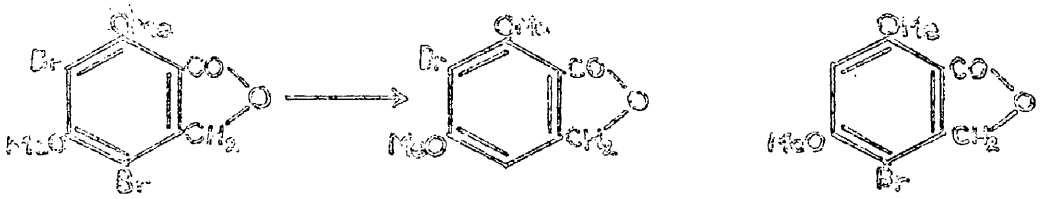
4,6-dibromo-5,7-dimethoxyphthalide (XXXVIII) was isolated.

Hydrolysis by aqueous dioxan has several advantages over alkaline hydrolysis. The product is easily isolated. Dioxan is distilled off under reduced pressure, and the material which precipitates out usually requires one crystallisation only to bring it to top purity. The yields are high, and there is no discolouration or decomposition of phenolic compounds. Three further examples of successful phthalide formation by aqueous dioxan hydrolysis are later described.

The preparation of 5,7-dihydroxyphthalide (XXXI) required the removal of the two bromine substituents from 4,6-dibromo--5,7-dihydroxyphthalide (XXXVI). Nuclear debromination of 4-bromo-5,7-dimethoxyphthalide (XXIII) was achieved by Logan and

Newbold[6] by hydrogenation at atmospheric pressure of a solution of the meterial in ethyl acetate, in the presence of palladised charcoal, and magnesium oxide to remove hydrogen bromide formed during the reaction. After hydrogenation of 4,6-dibromo-5,7-dihydroxyphthalide (XXXVI) under these conditions for 48 hours, the starting material was recovered unchanged.

Similar hydrogenation of 4,6-dibromo-5,7-dimethoxyphthalide (XXXVIII) gave not the expected 5,7-dimethoxyphthalide (XXIV), but a monobromodimethoxyphthalide. The m.p. of this compound was depressed on mixing with 4-bromo-5,7-dimethoxyphthalide (XXIII) prepared by Logan and Newbold,[8] and the two compounds had different infrared spectra. The compound was therefore formulated as 6-bromo-5,7-dimethoxyphthalide (XL). The

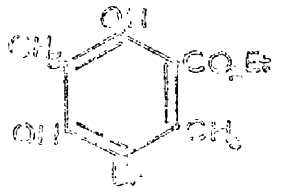


(XXXVIII) (XL) (XXIII)

6-bromine atom in (XXXVIII) is flanked on either side by a methoxyl group and is therefore sterically hindered. The 4-bromine atom is flanked by a methoxyl group and the methylene function of the phthalide ring. Due to strain in the 5-membered lactone ring, as shown by molecular models, the methylene group is bent away from the 4-bromine atom. Thus, although it is also doubly flanked the 4-bromine atom is less sterically hindered and more

readily removed than the 6-bromine atom.

Hydrogenation of 4,6-dibromo-5,7-dihydroxyphthalide (XXXVI) in the presence of platinum catalysts was also unsuccessful. Sonn[41] reports debromination of ethyl 3-bromo-4,6-dihydroxy-2,5-dimethylbenzoate (XLI) by hydrogenation of the material in solution in 2N aqueous sodium hydroxide, in the presence of

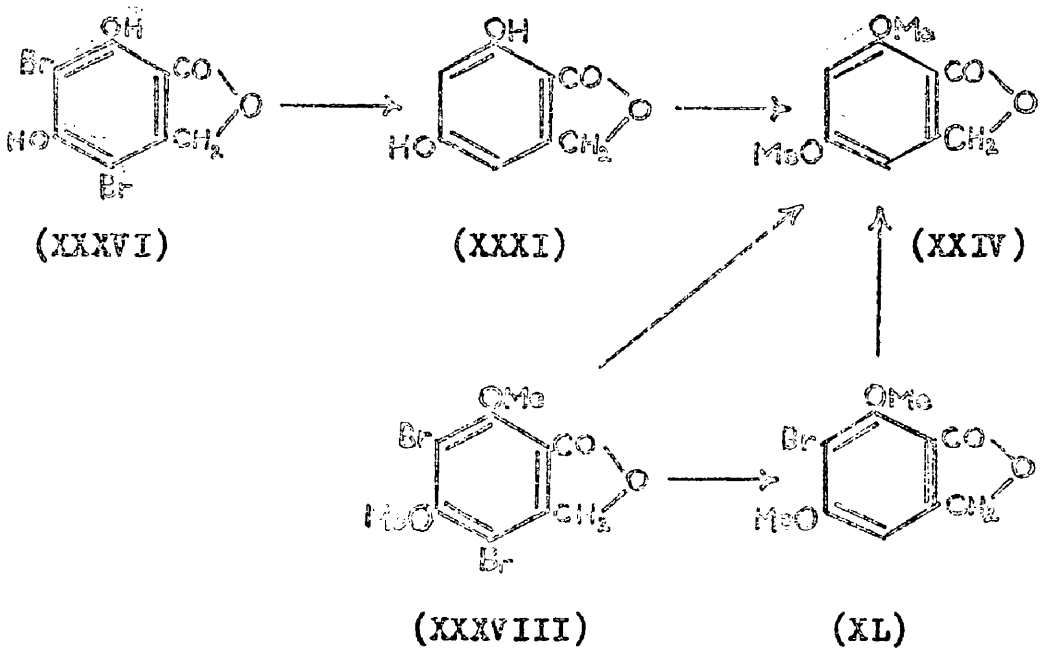


(XLI)

palladium hydroxide on calcium carbonate. Using commercial palladium hydroxide-calcium carbonate catalysts hydrogenation of (XXXVI) under these conditions for 48 hours returned starting material only. The catalyst used by Sonn was prepared by the method of Busch and Stove.[42] Using this latter catalyst hydrogenolysis of (XXXVI) was rapid and gave 5,7-dihydroxyphthalide (XXXI) without difficulty. Methylation of (XXXI) gave 5,7-dimethoxyphthalide (XXIV) previously prepared by Logan and Newbold.[8] Thus the product of the hydrogenolysis was confirmed to be 5,7-dihydroxyphthalide (XXXI).

4:6-Dibromo-5,7-dimethoxyphthalide (XXXVIII) and 6-bromo-5,7-dimethoxyphthalide (XL) were similarly debrominated using

the freshly prepared Busch and Stove catalyst to give 5,7--dimethoxyphthalide (XXIV).

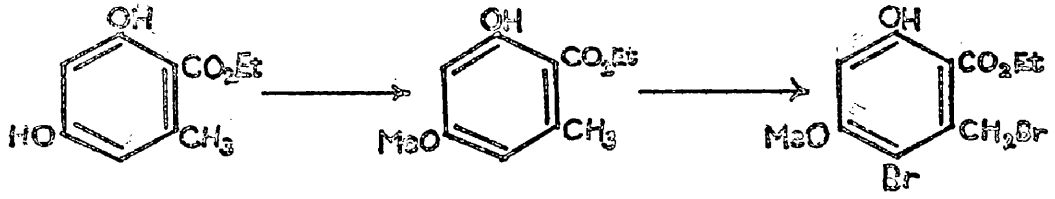


(XXXVI) (XXXI) (XXIV)

(XXXVIII) (XL)

Synthesis of 7-Hydroxy-5-methoxyphthalide (XXXII).

Ethyl everninate (XLIII) was prepared by treatment of ethyl orsellinate (XLII) with the theoretical amount of dimethyl sulphate.[43] Treatment of ethyl everninate with 2 mol. of bromine



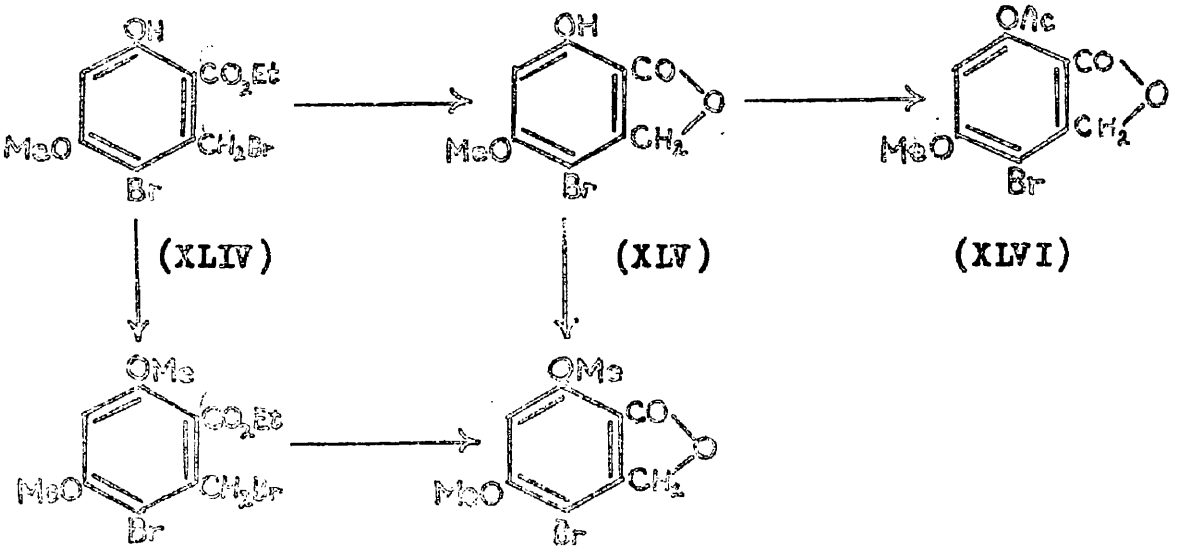
(XLII) (XLIII) (XLIV)

was first investigated. From consideration of the analogous

dibromination[6] of methyl orsellinate dimethyl ether (XXI), it can be deduced that the product will be ethyl 3-bromo-2-bromomethyl-6-hydroxy-4-methoxybenzoate (XLIV). On photobromination (XLIII) readily took up 1 mol. of bromine and a second mol. was taken up after a few hours. A third mol. was not taken up on prolonged treatment.

When (XLIV) was hydrolysed with aqueous dioxan, a phthalide formulated as 4-bromo-7-hydroxy-5-methoxyphthalide (XLV) was obtained in 86% yield. On hydrolysis of (XLIV) with aqueous sodium carbonate, there was some discolouration of the solution, and a 50% yield of the phthalide (XLV) was isolated. The phthalide (XLV) gave an acetate 7-acetoxy-4-bromo-5-methoxyphthalide (XLVI). Methylation of (XLV) gave 4-bromo-5,7-dimethoxyphthalide (XXIII) previously prepared by Logan and Newbold.[3] Since hydrolysis of (XLIV) to a phthalide took place, one bromine atom was located on the methyl side chain, and formation of (XXIII) proves the other to have been on the nucleus adjacent to the bromomethyl side chain. Thus the configuration of the bromine atoms in (XLIV) and (XLV) is confirmed.

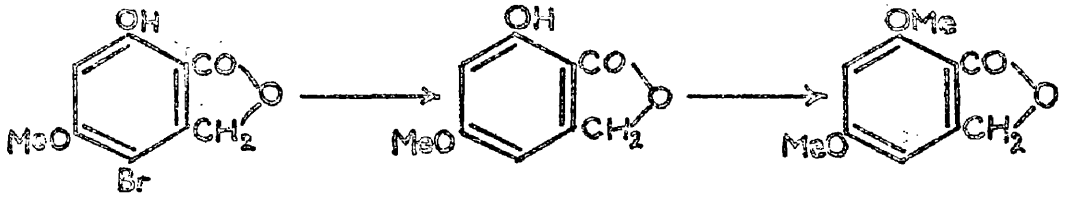
Methylation of ethyl 3-bromo-2-bromomethyl-6-hydroxy-4-methoxybenzoate (XLIV) gave a crystalline methyl ether ethyl 3-bromo-2-bromomethyl-4,6-dimethoxybenzoate (XLVII), which on hydrolysis with aqueous dioxan gave 4-bromo-5,7-dimethoxyphthalide (XXIII).



(XLIV) (XLV) (XLVI)

(XLVII) (XXIII)

4-Bromo-7-hydroxy-5-methoxyphthalide (XLV) was not debrominated by prolonged hydrogenolysis in the presence of palladised charcoal, but debromination of an alkaline solution in the presence of palladium hydroxide on calcium carbonate[42] was readily achieved. The product which on methylation gave

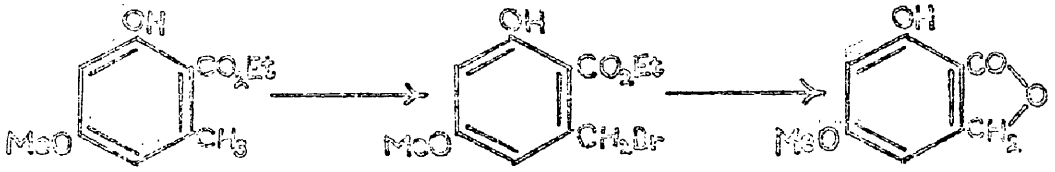


(XLV) (XXXII) (XXIV)

5,7-dimethoxyphthalide[8] (XXIV) was 7-hydroxy-5-methoxyphthalide (XXXII).

Photobromination of ethyl everninate (XLIII) with 1 mole of bromine gave a monobromo ethyl everninate, which on treatment

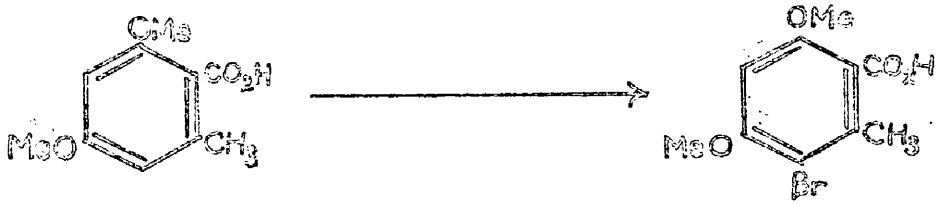
with aqueous dioxan gave a 90% yield of 7-hydroxy-5-methoxy-phthalide (XXXII). The bromine atom in the bromoester was therefore located in the methyl side chain and it was formulated



(XLIII) (XLVIII) (XXXII)

as ethyl 2-bromomethyl-6-hydroxy-4-methoxybenzoate (XLVIII).

Logan and Newbold[8] found that monophotobromination of orsellinic acid dimethyl ether (XXV) gave 3-bromo-4,6-dimethoxy--2-methylbenzoic acid (XXVI). The orientation of the bromine

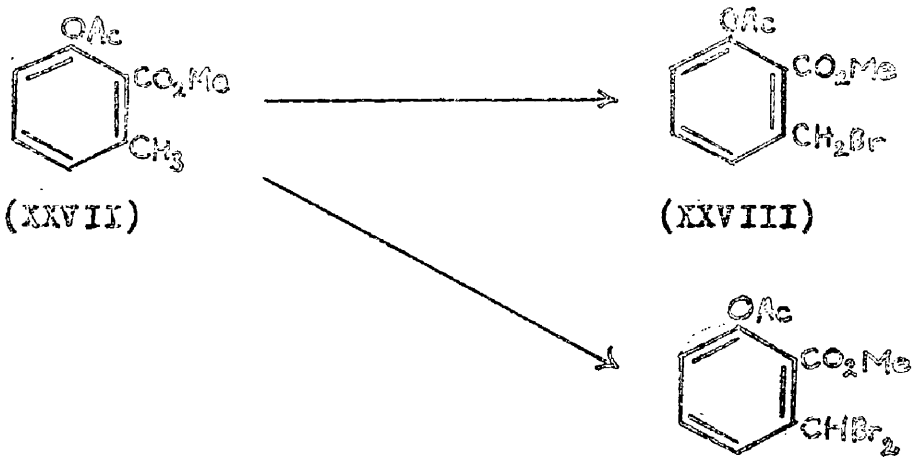


(XXV) (XXVI)

(XXI) (XXII)

atom was rigidly proved by degradative experiments. Photobromination of methyl orsellinate dimethyl ether (XXI) with 2 mol. of bromine gave methyl 3-bromo-2-bromomethyl-4,6-dimethoxybenzoate

(XXII). On the basis of these results they suggest[8] that bromination of the nucleus is required to activate the adjacent methyl group so that subsequent side chain bromination can take place. Our findings in the case of monophotobromination of (XLIII) suggest that no such activation of the side chain exists or is indeed necessary. Eliel et al[21] found that methyl 2--acetoxy-6-methylbenzoate (XXVII) on photobromination with 1 mole of bromine gave methyl 2-acetoxy-6-bromomethylbenzoate (XXVIII), while treatment with a further 1 mole of bromine gave methyl 2-acetoxy-6-dibromomethylbenzoate (XXIX).

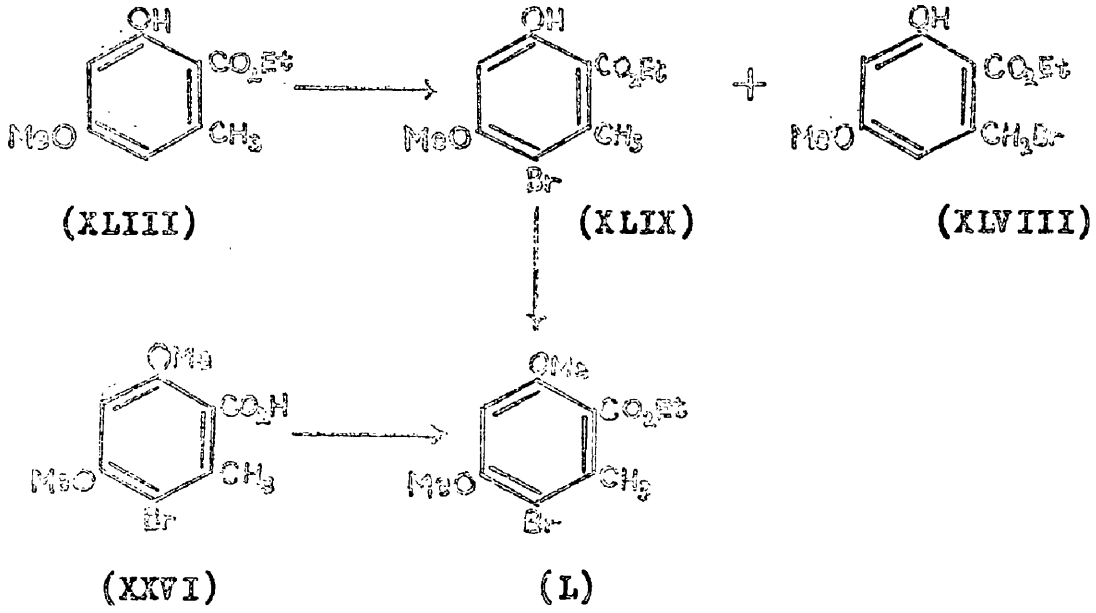


(XXVII) (XXVIII)

(XXIX)

When ethyl everninate (XLIII) was monophotobrominated under the usual conditions but with the addition of a trace of methanol to the solvent, we obtained a mixture of 2-isomeric monobromo-esters. The one which occurred in smaller amount was ethyl 2-bromomethyl-6-hydroxy-4-methoxybenzoate (XLVIII). The other gave a crystalline methyl ether.

Logan and Newbold[8] have prepared 3-bromo-4,6-dimethoxy--2-methylbenzoic acid (XXVI) of which a sample was available to us. Esterification of (XXVI) with diazoethane gave ethyl 3-bromo-4,6-dimethoxy-2-methylbenzoate (L) which was found to be



identical with the methyl ether of the bromo-compound. The monobromo-ethyl everninate was therefore formulated as ethyl 3-bromo-6-hydroxy-4-methoxy-2-methylbenzoate (XLIX).

On the basis of the work of Logan and Newbold[8], of Eliel et al.[20,21] and of this work, no rule can yet be laid down to predict the position at which the first molecule of bromine will enter substituted 2-methylbenzoic acids or substituted 2-methylbenzoic esters.

Intramolecular Hydrogen Bonding in 7-Hydroxyphthalides.

Examination of the 7-hydroxyphthalides prepared during

this work shows that carbonyl stretching frequencies are in agreement with the findings of Duncanson, Grove and Zealley.[40] They compared the carbonyl stretching frequencies of 7-hydroxyphthalides and 4-hydroxyphthalides in dilute solution, and found that due to intramolecular hydrogen bonding there was a characteristic lowering of the frequency of the former. In the solid state both showed lowered frequencies due to intermolecular hydrogen bonding. They also found that due to stronger intramolecular hydrogen bonding, the carbonyl frequencies of ortho-hydroxybenzoic esters were much lower still.

Duncanson, Grove and Zealley[40] have observed that due to strain in the lactone ring of a phthalide, as shown by molecular models, the carbonyl group is bent away from the 7-hydroxyl group to such an extent that the O-H-O distance approaches 3Å, the limit for hydrogen bond formation.[44] A bond of this length would thus be expected to be weak.

Table I lists the carbonyl stretching frequencies of phthalides prepared during this work, in the solid state as nujol mulls, and in dilute solution in chloroform. Values in carbon tetrachloride were not determined since several of the phthalides were completely insoluble in that solvent.

Table I.

	Nujol ($cm.^{-1}$)	Chloroform ($cm.^{-1}$)
4,6-Dibromo-5,7-dihydroxy-phthalide (XXXVI)	1715	1748
4-Bromo-7-hydroxy-5-methoxy-phthalide (XLV)	1733	1742
7-Hydroxy-5-methoxyphthalide (XXXII)	1733	1748
5,7-Dihydroxyphthalide (XXXI)	1724	1732
Phthalide (I),	1752	1761
4,6-Dibromo-5,7-dimethoxy-phthalide (XXXVIII)	1770	1776
4-Bromo-5,7-dimethoxyphthalide[8] (XXIII)	1767	1763
5,7-Dimethoxyphthalide[8] (XXIV)	1748	1761
6-Bromo-5,7-dimethoxy-phthalide (XL)	1736	1764
7-Acetoxy-4-bromo-5-methoxy-phthalide (XLVI)	1761	-
5,7-Diacetoxy-4,6-dibromo-phthalide (XXXVII)	1751	-

Because of intermolecular hydrogen bonding in the 7-hydroxyphthalides spectra of Nujol mulls do not reliably show the presence of intramolecular hydrogen bonding between the 7-hydroxy group and the carbonyl group. Values for (XLVI) and (XXXVII) in chloroform are not listed since the acetate and

phthalide bands in the carbonyl region of each were unresolved. The values for (XXXVIII) in both nujol and chloroform are high. This effect cannot be ascribed to steric factors, but may be due to the combined electron attractive effect of both bromine substituents on the carbonyl group.[60]

The difference between the carbonyl frequencies of the 7-hydroxyphthalides and the 7-methoxyphthalides is clearly shown in dilute solution in chloroform. The 7-hydroxyphthalides absorb in the range 1732-1748 $cm.^{-1}$, and phthalide (I) and the 7-methoxyphthalides excluding (XXXVIII), were in the range 1761-1764 $cm.^{-1}$

Table II

	Nujol $cm.^{-1}$	Chloroform $cm.^{-1}$
Ethyl 3,5-dibromo-2-bromomethyl--4,6-dihydroxybenzoate (XXXV)	1647	1667
Ethyl 2-bromomethyl-6-hydroxy-4--methoxybenzoate (XLVIII)	1650	1661
Ethyl 3-bromo-6-hydroxy-4-methoxy--2-methylbenzoate (XLIX)	1650	1655
Ethyl 3-bromo-2-bromomethyl-6--hydroxy-4-methoxybenzoate (XLIV)	1639	1661
Ethyl 3-bromo-2-bromomethyl-4,6--dimethoxybenzoate (XLVII)	1733	1724
Ethyl 3-bromo-4,6-dimethoxy-2--methylbenzoate (L)	1715	1721

The carbonyl maxima in chloroform of the ortho-hydroxybenzoate esters and the orthomethoxybenzoate esters prepared during this work are listed in Table II, the former showing maxima in the range 1655-1667 cm.$^{-1}$, and the latter in the range 1721-1724 cm.$^{-1}$

The carbonyl frequencies of the orthohydroxybenzoate esters, lowered by strong intramolecular hydrogen bonding, contrast with the higher carbonyl frequencies of the corresponding phthalides. The strength of the hydrogen bond is due partly to the fact that it is situated in an unstrained 6-membered ring. Both chemical and spectroscopic studies[45,46] have shown that this ring is further stabilised by resonance between the forms (LI) and (LII). The carbonyl absorption frequency of such compounds,

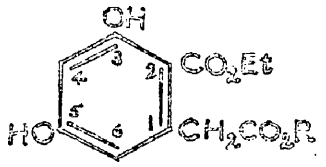
(LI) (LII)

and hence the degree of chelation, have been shown by Bellamy and Beecher[46] to be directly related to the double bond character of the ring double bond.

The orthomethoxybenzoic esters have a lower carbonyl frequency than non-hydrogen bonded phthalides since the ester holds the carbonyl group less rigidly than does the phthalide ring.

Thus, 7-hydroxyphthalides may be distinguished by their lower carbonyl stretching frequencies from phthalides having the 7-hydroxyl group protected. Also, phthalides which are not intramolecularly hydrogen bonded, may be distinguished from orthohydroxybenzoate esters or orthomethoxybenzoate esters by their higher carbonyl frequencies. The carbonyl frequencies of 7-hydroxyphthalides are too close to those of orthomethoxybenzoic esters to be distinguished from them.

Farmer, Hayes and Thomson[47] have expressed doubts as to the reliability of diazomethane for the detection of hydrogen bonded phenolic groups. Its action on 7-hydroxyphthalides and 5,7-dihydroxyphthalides, however, further illustrates the relatively weak nature of the intramolecular hydrogen bond in 7-hydroxyphthalides. Homophthalic acid derivatives of the type (LIII) can be selectively methylated by diazomethane [see Section II].



(R = H, Et or Me)

(LIII)

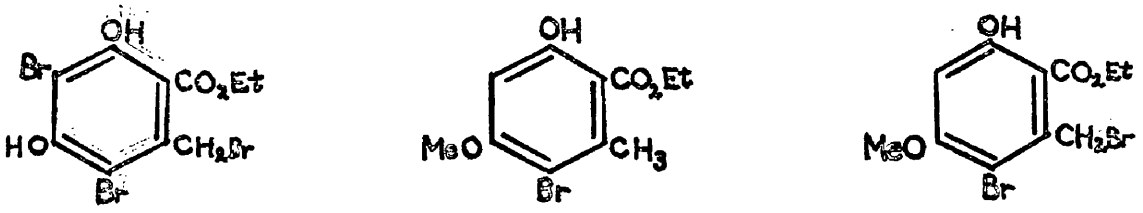
Methylation of the 5-hydroxyl group is complete in a few minutes, whereas the 3-hydroxyl group is only partially methylated by a 24 hour treatment with excess of the reagent. The inactivity of the 3-hydroxyl group in (LIII) can be ascribed to strong intramolecular hydrogen bonding with the ester carbonyl. Similarly, ethyl orsellinate (XLII) can be selectively methylated[66]

by diazomethane to give ethyl everninate (XLIII). In contrast,

(XLII) (XLIII)

selective methylation of the 5,7-dihydroxyphthalides (XXXI) and (XXXVI) is impossible, dimethylation by diazomethane being complete in both cases within 1 hour. The 7-hydroxyls of the 7-hydroxyphthalides (XXXII) and (XLV) were similarly readily methylated. Thus the 7-hydroxyl group of the 7-hydroxyphthalides does not show the inactivity to methylation with diazomethane which is associated with strong intramolecular hydrogen bonding.

It is interesting to note that selective methylation of ethyl 3,5-dibromo-2-bromomethyl-4,6-dihydroxybenzoate (XXXV) with diazomethane was impossible, and that dimethylation was complete within 4 hours. Similarly the hydrogen bonded 6-hydroxyl group



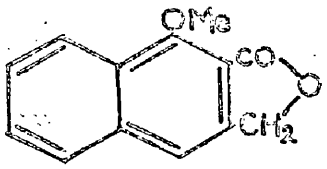
(XXXV) (XLIX) (XLIV)

in ethyl 3-bromo-6-hydroxy-4-methoxy-2-methylbenzoate (XLIX) and in ethyl 3-bromo-2-bromomethyl-6-hydroxy-4-methoxybenzoate (XLIV)

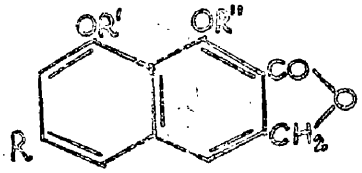
was methylated in from 2 to 4 hours. This is in sharp contrast with the inactivity of the 3-hydroxyl group in (LIII) and the 2-hydroxyl group in ethyl orsellinate (XLII). Clearly the greater acidity of the 6-hydroxyl group in (XXXV), (XLIX) and (XLIV) due to ring deactivation by the bromine atoms, partly overcomes the inactivity of the hydroxyl due to intramolecular hydrogen bond formation.

INTRODUCTION (b)

In view of the success of the aqueous dioxan method, described earlier in this section, of preparing phthalides from orthobromomethyl esters, it was decided to attempt to extend the existing methods to the synthesis of 7-methoxybenzo[1',2',5,6] phthalide (LIV). Interest in this type of compound was also occasioned by the fact that two naturally occurring phthalides of this type, α-soriganin and β-soriganin, obtained from the bark of Rhomnus japonica,[4,5] have recently been the subject of considerable structural investigation.[6,7] The studies of Nikuni and his co-workers[4,5,6,7] have shown the structures of α- and β-soriganin to be almost certainly (VII, R = OMe, R' = R'' = H) and (VII, R = R' = R'' = H) respectively. Synthetic confirmation of these structures is, however, still required.



(LIV)

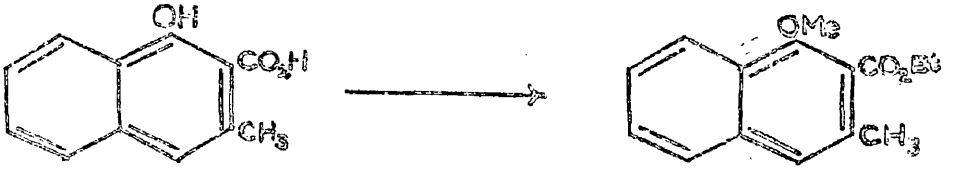


(VII)

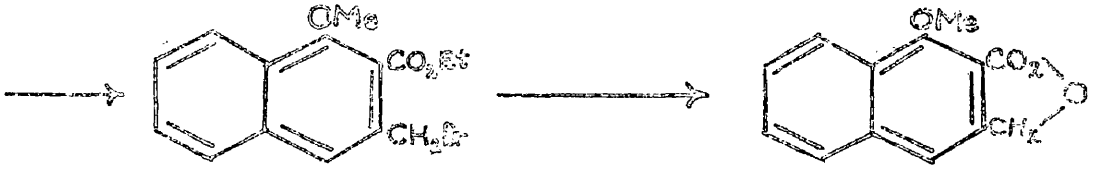
Since starting material for the synthesis of 7-methoxybenzo[1',2',5,6]phthalide (LIV) appeared to be readily obtainable, it was proposed firstly to synthesise (LIV) to determine if the route were feasible, and if it were, to extend it to the synthesis of α-soriganin methyl ether (VII, R = OMe, R' = R'' = Me) and β-soriganin methyl ether (VII, R = H, R' = R'' = Me). The

synthesis of (LIV) required 1-hydroxy-3-methyl-2-naphthoic acid (LV) as starting material, esterification and methylation of which would have given ethyl 1-methoxy-3-methyl-2-naphthoate (LVI).

Photobromination of (LVI) would convert the methyl to bromomethyl to give ethyl 3-bromomethyl-1-methoxy-2-naphthoate (LVII). Bromine might also be introduced into the nucleus,



(LV) (LVI)

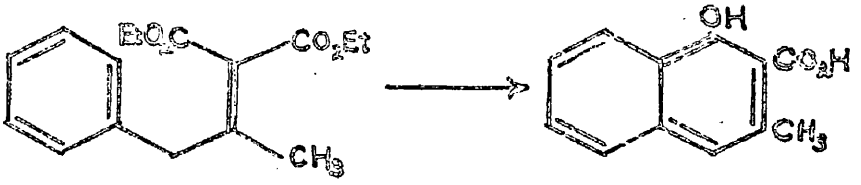


(LVII) (LIV)

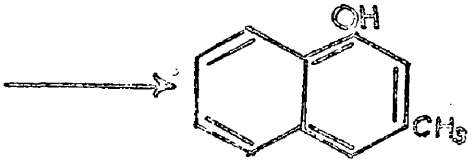
but as was found in the earlier part of this section, no rule can be laid down to predict which position the first molecule of bromine will attack. Treatment of (LVII) with aqueous dioxan would form the phthalide (LIV) and nuclear bromine substituents could be finally removed by catalytic hydrogenation.

Preparation of the starting material 1-hydroxy-3-methyl--2-naphthoic acid (LV) is described by Kon and Speight,[48] and in

greater detail by Marion and McRae.[49] Phenylacetone and diethyl malonate are condensed in the presence of zinc chloride-aniline complex to give ethyl 2-ethoxycarbonyl-3-methyl-4-phenyl-2--butenoate (LVIII). Treatment of the ester (LVIII) with alkali gives an acidic product. Marion and McRae[49] claim to have proved that this acid is 1-hydroxy-3-methyl-2-naphthoic acid (LV). They describe decarboxylation of this compound in the presence of copper and quinoline to give a product which they maintain was identical with a sample of 3-methyl-1-naphthol (LIX) synthesised by an unambiguous route.



(LVIII) (LV)



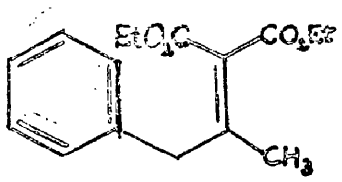
(LIX)

It was found, however, that Marion and McRae's method did not produce (LV), but a different acidic product. Careful examination of the reaction mixture failed to show the presence of any 1-hydroxy-3-methyl-2-naphthoic acid (LV). The proposed synthesis was therefore pursued no further, but the nature of the acidic product and the mechanism of its formation were investigated.

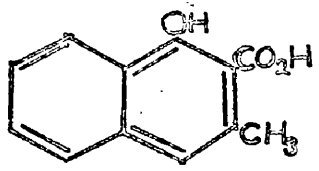
THEORETICAL (b)

Action of Alkali on Ethyl 2-Ethoxycarbonyl-3-methyl-4-phenyl--2-butenoate (LVIII).

The synthesis of 7-methoxybenzo[1',2',5,6]phthalide (LIV) proposed in the introduction, required 1-hydroxy-3-methyl--2-naphthoic acid (LV) as starting material. Marion and McRae[49] describe the preparation of (LV) by treatment of ethyl 2-ethoxycarbonyl-3-methyl-4-phenyl-2-butenoate (LVIII) with alkali. Ethyl 2-ethoxycarbonyl-3-methyl-4-phenyl-2-butenoate (LVIII) was prepared as they describe. Phenylacetone and diethyl malonate were condensed in the presence of zinc chloride-aniline complex to give the oily ester (LVIII) in 10% yield.



(LVIII)



(LV)

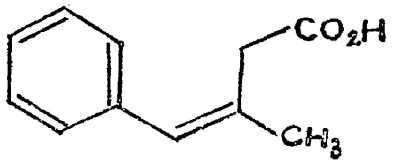
Three different batches of the ester (LVIII) were prepared exactly as Marion and McRae describe. The fraction from each, boiling in the range 172-175°/3 m.m., and the crude material from each, were treated separately with 10% aqueous alcoholic alkali as described. In each case a high yield of an acidic compound, 'Acid A', m.p. 152-154° (decomp.) was obtained. The m.p. of (LV) is given as 194° (decomp.). Other strengths of aqueous alcoholic alkali from 5% to 15% were

tried for varying periods of time, but with the same result. The materials from all mother liquors, in ethanol, gave no colour with aqueous ferric chloride.

Structure of 'Acid A'.

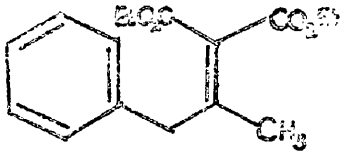
'Acid A' dissolved with vigorous effervescence in cold aqueous sodium hydrogen carbonate. It decolourised bromine water, and on oxidation with a slight excess of aqueous alkaline potassium permanganate gave benzaldehyde. It analysed for $C_{12}H_{12}O_4$ and its titration equivalent was 106. Thus 'Acid A' had an aromatic ring with one substituent, a side chain, unsaturated α, β to the ring, and having two carboxyl groups on it.

On heat treatment 'Compound A' lost carbon dioxide and an acidic crystalline product 'Acid B' m.p. 112-114° was obtained 'Acid B' also dissolved, but less vigorously, in cold aqueous sodium hydrogen carbonate, decolourised bromine water, and on oxidation with aqueous alkaline potassium permanganate gave benzaldehyde. It analysed for $C_{11}H_{12}O_2$ and had titration equivalent 177. 'Acid B' thus had an aromatic ring with one substituent, a side chain, unsaturated α,β to the ring, and having one carboxyl group on it. Its light absorption in ethanol showed a maximum at 2460 Å (ε = 14,900) 'Acid B' was therefore, identified as 3-methyl-4-phenyl-3-butenoic acid (LX) for which Moore[80] gives m.p. 112-113° and light absorption in ethanol at

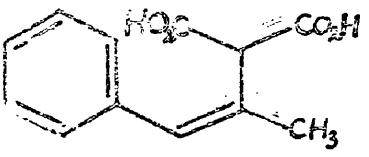


(LX)

2450A. (ε = 14,600), and Salomon and Fittig[51] give m.p. 113°.



(LVIII)



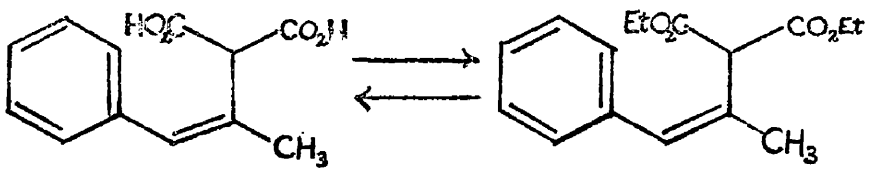
(LXI)

From the foregoing evidence the acid m.p 152-154° (decomp.) is 2-carboxy-3-methyl-4-phenyl-3-butenoic acid (LXI).

Treatment of ethyl 2-ethoxycarbonyl-3-methyl-4-phenyl--2-butenoate (LVIII) with alkali has not caused cyclisation, as Marion and McRae claim, but has hydrolysed it to the diacid, with a simultaneous shift of the double bond. A malonic acid derivative of this type would be expected to decarboxylate readily, hence the formation of 3-methyl-4-phenyl-3-butenoic acid (LX).

By treatment of (LXI) with diazoethane the ester ethyl 2-ethoxycarbonyl-3-methyl-4-phenyl-3-butenoate (LXII) was obtained. This ester had different b.p., infrared and ultraviolet absorption spectra from ethyl 2-ethoxycarbonyl-3-methyl--4-phenyl-2-butenoate (LVIII). Treatment of (LXII) with alkali under the conditions employed for the hydrolysis of (LVIII) to the acid (LXI), also gave (LXI) in good yield. The material from the mother liquors, in ethanol, gave no colouration with aqueous ferric chloride. Thus with ethyl 2-ethoxycarbonyl-3--methyl-4-phenyl-3-butenoate (LXII) as with the ester (LVIII), no cyclisation to a naphthalene derivative takes place, and the possibility that Marion and McRae had been dealing with this

ester when they found cyclisation taking place is ruled out.

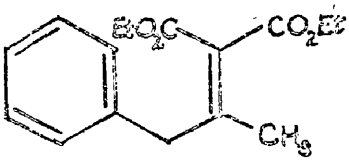
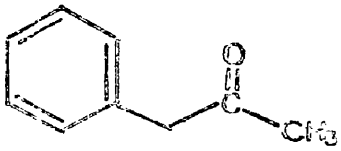
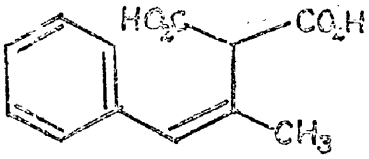
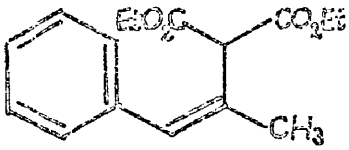
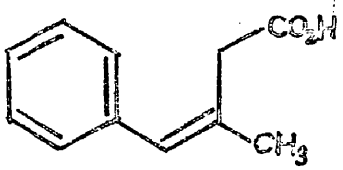


(LXI) (LXII)

It was now fairly certain that the double bond in the acid m.p. 152-154° (Decomp.) was α, β to the aromatic ring, and that it could be represented by (LXI), but it seemed to us necessary to prove that the double bond in the ester (LVIII) as prepared by Marion and McRae, and Kon and Speight, was indeed β, γ to the ring as they assume it to be. The products of oxidations with a slight excess of aqueous alkaline potassium permanganate on ethyl 2-ethoxycarbonyl-3-methyl-4-phenyl-2-butenoate (LVIII), phenylacetone (LXIII), 2-carboxy-3-methyl-4-phenyl-3-butenoic acid (LXI), ethyl 2-ethoxycarbonyl-3-methyl-4-phenyl-3-butenoate (LXII), and 3-methyl-4-phenyl-3-butenoic acid (LX) were examined. The results of the oxidations are summarised in Table III.

Thus in the case of (LXI) (LXII) and (LX) the double bond is definitely fixed as being α, β to the aromatic ring. The position of the double bond in (LX) is in any case known. The experiments are, however, inconclusive in fixing the position of the double bond in (LVIII), since phenylacetone (LXIII) the expected product, would be further oxidised to benzoic acid.

Table III.

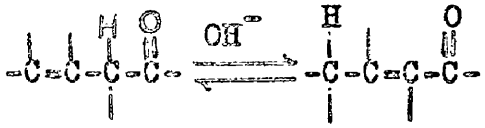
	Light Absorption in Ethanol	Neutral Fraction	Acidic Fraction
 (LVIII)	2230 Å	-	Benzoic acid
 (LXIII)	——	-	Benzoic acid
 (LXI)	2470 Å	Benzaldehyde	-
 (LXII)	2470 Å	Benzaldehyde	-
 (LX)	2460 Å	Benzaldehyde	-

On treatment of (LVIII) with the theoretical amount of ozone, however, phenylacetone was isolated. Thus the position of the double bond in ethyl 2-ethoxycarbonyl-3-methyl-4-phenyl-2--butenoate (LVIII) is fixed as β,γ to the benzene ring.

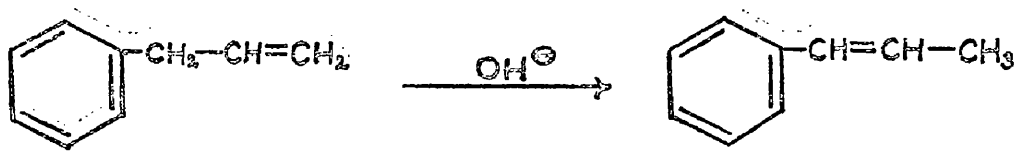
It is of interest to note that the ultraviolet absorption spectra also confirm the positions assigned to the double bonds. The compounds each contain three chromophoric centres, the aromatic ring, the double bond, and the ester or acid carbonyls. Since the aromatic ring has a greater conjugating effect than the carbonyls, the compounds (LXI), (LXII) and (LX) having the double bond in conjugation with the aromatic ring are expected to show absorption at a longer wavelength than (LVIII) in which the double bond is in conjugation with the ester carbonyls.[52] In practice this was found to be the case (LXI), (LXII) and (LX) showing a band in the range 2460-2470 Å, while (LVIII) shows a band at 2230 Å. (see Table III).

Mechanism of Reaction.

When an α,β or β,γ unsaturated compound is heated with strong alkali, an equilibrium is often established between the two isomers.



For example allylbenzene (LXIV) is transformed almost irreversibly into propenylbenzene (LXV).[53]



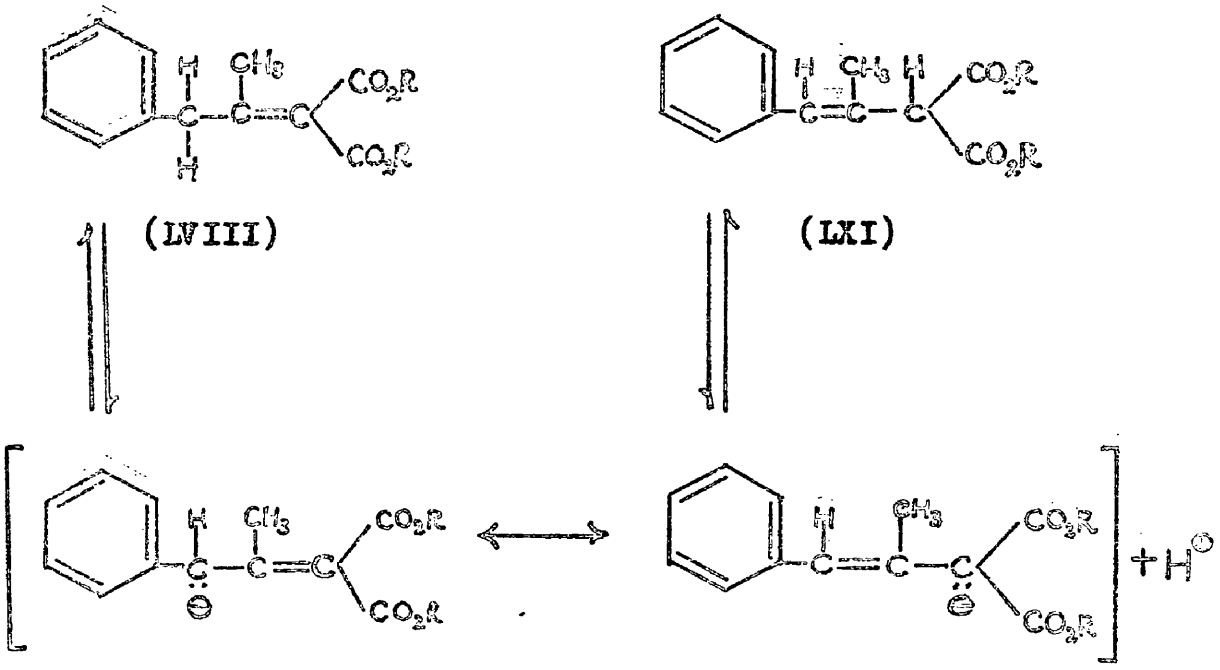
(LXIV) (LXV)

Exchange reactions with deuterium oxide[54,55,56] have shown that an equilibrium is set up via a common carbanion, obtained by attack of the base on a hydrogen atom attached to a carbon atom α to the unsaturated group.

The results of such equilibria can usually be predicted by consideration of hyperconjugation and resonance.[57] If a common carbanion is involved in the isomerisation, it is expected that the olefin to predominate from it will be that which is more stabilised by resonance. Thus 2-carboxy-3-methyl--4-phenyl-3-butenoic acid (LXI) has a structure more favoured by resonance than ethyl 2-ethoxycarbonyl-3-methyl-4-phenyl-2-butenoate (LVIII) since the double bond in (LXI) is α, β to the aromatic ring, and the aromatic ring has a greater conjugating effect than the carbonyls.

Hyperconjugation also exerts an influence on such equilibria,[57] the equilibrium shifting in the direction in which the double bond will become conjugated with the greatest number

of α-hydrogen atoms. Considering hyperconjugation only, (LVIII) is slightly the more favoured structure since the double bond is in conjugation with five hydrogen atoms, whilst in (LXI) the double bond is in conjugation with four hydrogen atoms. The hyperconjugation effect, however, is weak and exerts its influence only when no other stronger factor is present. In the present case the strong conjugating effect of the aromatic ring predominates. The isomerisation may be outlined as follows:



(LVIII) (LXI)

Whether the isomerisation takes place before or after the removal of the ester groups by hydrolysis does not alter the principles involved.

EXPERIMENTAL

All melting points are uncorrected. Ultraviolet absorption spectra were determined in ethanol solution.

Ethyl 3,5-dibromo-2-bromomethyl-4,6-dihydroxybenzoate (with J. Highet). - A solution of ethyl 3,5-dibromo-4,6-dihydroxy--2-methylbenzoate (10 g.) in dry carbon tetrachloride (150 c.c.) in a quartz flask, heated under reflux by irradiation from a 150 w. lamp, was treated dropwise with bromine (4.52 g.) in dry carbon tetrachloride (20 c.c.) during 30 minutes. Refluxing was continued for a further 10 minutes. The solvent was removed under reduced pressure and the resulting gum was crystallised from light petroleum (b.p. 60-80°) to give ethyl 3,5-dibromo-2-bromomethyl-4,6-dihydroxybenzoate (11.7 g.) as stout needles m.p. 122-123°.

Found: C,28.1; H,2.3%

$C_{10}H_9O_4Br_3$ requires: C,27.7; H,2.1%

Light absorption: λ max. 2070 Å.(ε = 10,700), 2340 Å.(ε = 15,800), 2680 Å. (ε = 9,000) and 3350 Å (ε = 6,400).

Infrared spectrum: in nujol ν max. 1647 $cm.^{-1}$ (H-bonded ester), in chloroform ν max. 1667 $cm.^{-1}$ (H-bonded ester).

The compound in ethanol solution gave a deep purple colour with aqueous ferric chloride.

4,6-Dibromo-5,7-dihydroxyphthalide (a) (with J. Highet). - Ethyl 3,5-dibromo-2-bromomethyl-4,6-dihydroxybenzoate (1.36 g.) in solution in 10% aqueous sodium carbonate (136 c.c.) was heated

for 1 hour on a steam bath. The solution rapidly became dark brown in colour. The cooled solution was acidified (Congo red) with concentrated hydrochloric acid, and extracted with chloroform (3 x 20 c.c.). The combined yellow chloroform extract was washed with aqueous sodium hydrogen carbonate (3 x 20 c.c.) and the alkaline washings acidified (Congo red) with concentrated hydrochloric acid. Extraction of the acidified solution with chloroform (6 x 15 c.c.) followed by evaporation of the dried (Na_2SO_4) extract under reduced pressure gave a brown solid. Crystallisation of the solid from chloroform gave 4,6-dibromo-5,7-dihydroxyphthalide (100 mg., 10%) as prisms, m.p. 236-238° (decomp.).

Found: C,29.79; H,1.38%

$C_8H_4O_4Br_2$ requires: C,29.7; H,1.30%

Light absorption: λ max. 2240 Å. (ε = 38,100) and 3040 Å. (ε = 9,400) and inflexion at 2120 Å. (ε = 14,000).

Infrared spectrum: in nujol ν max. 1715 $cm.^{-1}$ (H-bonded phthalide carbonyl), chloroform ν max. 1748 $cm.^{-1}$ (H-bonded phthalide carbonyl).

The compound in ethanol gave a deep purple colour with aqueous ferric chloride.

(b) Ethyl 3,5-dibromo-2-bromomethyl-4,6-dihydroxybenzoate (1 g.) was dissolved in methanol (40 c.c.) and water (30 c.c.) added. The solution was refluxed for 6 hours. The methanol was removed under reduced pressure and the solution allowed to cool. The

white precipitate was filtered off, sucked dry, and heated on a steam bath for a few minutes with benzene (20 c.c.). The mixture was cooled, the white solid was filtered off and crystallised from chloroform to give 4,6-dibromo-5,7-dihydroxy phthalide (180 mg., 24%) as small prisms, m.p. 236-238°.

(c) The same product was obtained in 55% yield by similar treatment of ethyl 3,5-dibromo-2-bromomethyl-4,6-dihydroxybenzoate with aqueous ethanol. Similar treatment with absolute methanol and absolute ethanol also gave 4,6-dibromo-5,7-dihydroxyphthalide in 20% and 45% yields respectively. The identity of the products was established by mixed m.p. and comparison of the infrared spectra.

(d) Ethyl 3,5-dibromo-2-bromomethyl-4,6-dihydroxybenzoate (1 g.) was dissolved in dioxan (20 c.c.) and water (20 c.c.) added. The solution was refluxed for 24 hours, the dioxan was removed under reduced pressure and the solution cooled. The white solid was filtered off, sucked dry and crystallised from chloroform to give 4,6-dibromo-5,7-dihydroxyphthalide (680 mg., 91%) as prisms, m.p. 236-238°.

(e) Ethyl 3,5-dibromo-2-bromomethyl-4,6-dihydroxybenzoate (1 g.) was refluxed for 24 hours with dioxan (40 c.c.), water (33 c.c.) and concentrated hydrochloric acid (3.5 c.c.). The product was worked up in the usual manner to give 4,6-dibromo-5,7--dihydroxyphthalide (120 mg., 16%).

5,7-Diacetoxy-4,6-dibromophthalide. - 4,6-Dibromo-5,7--dihydroxyphthalide (600 mg.) in solution in pyridine (1 c.c.) and acetic anhydride (10 c.c.) was heated for 2 hours on a steam bath. Water (100 c.c.) was added, and the solution warmed for a few minutes. On cooling, a white crystalline precipitate separated. The crystals were filtered off, washed with water and sucked dry. The material was recrystallised from methanol to give 5,7-diacetoxy-4,6-dibromophthalide (550 mg.) as plates, m.p. 162.5-164.5°

Found: C,35.60; H,2.13%.

$C_{12}H_8O_6Br_2$ requires: C,35.31; H,1.98%

Light absorption: λmax. 2170 Å. (ε = 41,500) and 2960 Å. (ε= 2,600).

Infrared spectrum: ν max. in nujol 1775 cm.$^{-1}$ (acetate) and 1751 cm.$^{-1}$ (phthalide), ν max. in chloroform 1779 cm.$^{-1}$ (acetate and phthalide carbonyls).

4,6-Dibromo-5,7-dimethoxyphthalide from 4,6-dibromo-5,7--dihydroxyphthalide. - A solution of 4,6-dibromo-5,7-dihydroxy-phthalide (1 g.) in methanol (40 c.c.) was treated for 1 hour with excess ethereal diazomethane. The solvents were removed to yield a colourless gum which crystallised from chloroform-methanol to give 4,6-dibromo-5,7-dimethoxyphthalide (1.02 g.) as needles, m.p. 136.5-138.5°.

Found: C,33.86; H,2.42%.

$C_{10}H_8O_4Br_2$ requires: C,34.12; H,2.29%.

Light absorption: λ max. 2220 Å. (ε = 40,200) and 3020 Å. (ε = 2,400).

Infrared spectrum: in nujol ν max. 1770 $cm.^{-1}$ (phthalide carbonyl), in chloroform ν max. 1776 $cm.^{-1}$ (phthalide carbonyl).

Ethyl 3,5-dibromo-2-bromomethyl-4,6-dimethoxybenzoate. - A solution of ethyl 3,5-dibromo-2-bromomethyl-4,6-dihydroxybenzoate (700 mg.) in ether (10 c.c.) and methanol (1 c.c.) was treated with excess ethereal diazomethane until the solute in ethanol gave no colour with aqueous ferric chloride (4 hours). Removal of the solvents gave ethyl 3,5-dibromo-2-bromomethyl-4,6-dimethoxybenzoate as a colourless oil.

Infrared spectrum of the oil ν max. 1721 $cm.^{-1}$ (ester carbonyl).

4,6-Dibromo-5,7-dimethoxyphthalide from Ethyl 3,5-dibromo-2-bromomethyl-4,6-dimethoxybenzoate. - To a solution of ethyl 3,5-dibromo-2-bromomethyl-4,6-dimethoxybenzoate (350 mg.) in dioxan (20 c.c.) was added water (10 c.c.) and the resulting solution refluxed gently for 24 hours. The dioxan was removed under reduced pressure and the solution cooled. The white solid was filtered off, sucked dry, and crystallised from chloroform-methanol to give 4,6-dibromo-5,7-dimethoxyphthalide (244 mg., 85%) as felted needles m.p. 136-138.5°. The infrared spectra of the compound and of the same compound prepared above were identical.

6-Bromo-5,7-dimethoxyphthalide. - A solution of 4,6-dibromo-5,7-dimethoxyphthalide (200 mg.) in dry ethyl acetate (50 c.c.) was shaken with hydrogen at room temperature and atmospheric pressure in the presence of palladised charcoal (200 mg.; 2.5% of palladium chloride on charcoal) and magnesium oxide (400 mg.). When absorption of hydrogen was complete (ca. 20 hours) the mixture was filtered and the insoluble residue extracted with boiling chloroform (100 c.c.) and again filtered. The combined filtrates were evaporated under reduced pressure to give a white solid which was crystallised from chloroform-methanol to give 6-bromo-5,7-dimethoxyphthalide (70 mg.) as blades, m.p. 207-209°. The m.p. of the compound on admixture with 4-bromo-5,7-dimethoxyphthalide (lit.[8], m.p. 246-248°) was depressed to 180-200°.

Found: C,43.98; H,3.30%

$C_{10}H_9O_4Br$ requires: C,43.98; H,3.33%.

Light absorption: λ max. 2190 Å. (ε = 32,900) and 2570 Å. (ε = 12,200) and inflexion at 2870 Å. (ε = 1,500)

Infrared spectrum: in nujol ν max. 1736 cm.$^{-1}$ (phthalide carbonyl), in chloroform ν max. 1764 cm.$^{-1}$ (phthalide carbonyl).

The same yield of 6-bromo-5,7-dimethoxyphthalide was obtained when 4,6-dibromo-5,7-dimethoxyphthalide was hydrogenated under identical conditions for 48 hours.

Attempted debromination of 4,6-dibromo-5,7-dihydroxyphthalide. - A solution of 4,6-dibromo-5,7-dihydroxyphthalide (200 mg.) in dry ethyl acetate (50 c.c.) was shaken with hydrogen at room

temperature and atmospheric pressure in the presence of palladised charcoal (200 mg., 2.5% of palladium chloride on charcoal) for 48 hours. The mixture was filtered and the filtrate evaporated to dryness to give a brown gum (20 mg.). The solid residue of catalyst and magnesium oxide was acidified, and the mixture extracted with boiling chloroform (4 x 40 c.c.). The combined chloroform extract was washed with water and dried (Na_2SO_4). Evaporation of the chloroform under reduced pressure gave a pale yellow solid. The solid crystallised from chloroform to give starting material 4,6-dibromo-5,7-dihydroxyphthalide (150 mg.) as prisms, m.p. 236-238° (decomp.). The m.p. of the material was undepressed on admixture with the starting material.

5,7-Dihydroxyphthalide. - A solution of 4,6-dibromo-5,7--dihydroxyphthalide (500 mg.) in aqueous sodium hydroxide (10 c.c., 2N) was shaken with hydrogen at room temperature and atmospheric pressure in the presence of palladised calcium carbonate[62] (1 g., 2% palladium hydroxide on calcium carbonate). When absorption of hydrogen was complete (ca. 30 minutes) the mixture was filtered, and the filtrate acidified (Congo red) with concentrated hydrochloric acid. The white solid which slowly separated was filtered off, washed with water and sucked dry. Crystallisation from aqueous methanol gave 5,7-dihydroxyphthalide (200 mg., 80%) as blades, m.p. 253-260° (darkens at 235°), m.p. 257-260° (in vacuo).

Found: C,57.68; H,3.84%

$C_8H_6O_4$ requires: C,57.83; H,3.64%

Light absorption: λ max. 2160 Å. (ε = 35,300), 2550 Å. (ε = 15,000) 2900 Å. (ε = 5,000).

Infrared spectrum: in nujol ν max. 1724 $cm.^{-1}$ (phthalide carbonyl) in chloroform 1732 $cm.^{-1}$ (phthalide carbonyl).

The compound in ethanol gave a purple colour with aqueous ferric chloride.

5,7-Dimethoxyphthalide from 5,7-dihydroxyphthalide. - A solution of 5,7-dihydroxyphthalide (100 mg.) in methanol (10 c.c.) was treated with excess ethereal diazomethane until the solute in ethanol gave no colour with aqueous ferric chloride (ca. 1 hour). Removal of the solvents under reduced pressure gave a colourless gum which rapidly crystallised. Recrystallisation from chloroform-methanol gave needles m.p. 151-153°. The m.p. of the material was undepressed on admixture with an authentic sample of 5,7-dimethoxyphthalide m.p. 151-153° prepared by Logan and Newbold.[8] The infrared spectra in nujol of the two specimens were identical.

5,7-Dimethoxyphthalide from 4,6-dibromo-5,7-dimethoxyphthalide. A solution of 4,6-dibromo-5,7-dimethoxyphthalide (250 mg.) in aqueous sodium hydroxide (15 c.c., 2N) was shaken with hydrogen at room temperature and atmospheric pressure in the presence of palladised calcium carbonate[42] (500 mg., 2% palladium hydroxide on calcium carbonate). When absorption of hydrogen was complete

(ca. 1 hour) the mixture was filtered, and the filtrate acidified (Congo red) with concentrated hydrochloric acid. The white solid which slowly separated was filtered off, washed with water and sucked dry. The solid was crystallised from chloroform-methanol to give needles, m.p. 151-153° (Logan and Newbold[0] give m.p. 151-153°). The m.p. was undepressed on admixture with an authentic specimen of 5,7-dimethoxyphthalide. The infrared spectra of the two specimens were identical.

5,7-Dimethoxyphthalide from 6-bromo-5,7-dimethoxyphthalide. - A solution of 6-bromo-5,7-dimethoxyphthalide (50 mg.) in aqueous sodium hydroxide (5 c.c., 2N) was shaken with hydrogen at room temperature and atmospheric pressure in the presence of palladised calcium carbonate[42] (100 mg.). When absorption of hydrogen was complete (ca. 1 hour) the mixture was filtered, and the filtrate acidified (Congo red) with concentrated hydrochloric acid. The white precipitate was filtered off, washed with water and sucked dry. Crystallisation from chloroform-methanol gave needles, m.p. 151-153°. The material was identical with 5,7-dimethoxyphthalide, by mixed m.p. and infrared comparison.

Ethyl 3-Bromo-2-bromomethyl-6-hydroxy-4-methoxybenzoate. - A solution of ethyl 6-hydroxy-4-methoxy-2-methylbenzoate [ethyl everninate] (5.005 g.) in dry carbon tetrachloride (75 c.c.) in a quartz flask, heated under reflux by irradiation from a 150 w. lamp was treated dropwise with bromine (7.61 g., 2 mols.) in dry

carbon tetrachloride (20 c.c.). Each addition was made when the colour of the previous addition had almost disappeared. For the addition of the bromine 6 hours was required. The solution was refluxed for a further 30 minutes. The solvent was removed under reduced pressure and the resulting gum which crystallised on cooling was recrystallised from light petroleum (b.p. 60-80°) to give ethyl 3-bromo-2-bromomethyl-6-hydroxy-4-methoxybenzoate (5.3 g.) as fine needles, m.p. 103.5-105°.

Found: C,35.79; H,3.41%

$C_{11}H_{12}O_4Br_2$ requires: C,35.90; H,3.30%.

Light absorption: λ max. 2280 Å. (ε = 28,600) and 3220 Å. (ε = 5,800), inflexion at 2090 Å. (ε = 15,200) and 2640 Å. (ε = 7,100).

Infrared spectrum: in nujol ν max. 1639 $cm.^{-1}$ (H-bonded ester), in chloroform ν max. 1661 $cm.^{-1}$ (H-bonded ester).

The compound in ethanol gave a purple colour with aqueous ferric chloride.

4-Bromo-7-hydroxy-5-methoxyphthalide. - (a) To a solution of ethyl 3-bromo-2-bromomethyl-6-hydroxy-4-methoxybenzoate (1.8 g.) in dioxan (60 c.c.) was added water (40 c.c.) and the solution gently refluxed for 24 hours. The dioxan was removed under reduced pressure and the solution cooled. The white precipitate was filtered off and sucked dry. The solid crystallised from chloroform to give 4-bromo-7-hydroxy-5-methoxyphthalide (1.1 g., 88%) as small prisms, m.p. 236-238° (decomp.).

Found: C,41.64; H,2.85; Br,30.72%

$C_9H_7O_4Br$ requires: C,41.72; H,2.73; Br,30.86%.

Light absorption: λ max. 2200 Å. (ε = 34,000), 2470 Å. (ε = 10,100) and 3000 Å. (ε = 4,200).

Infrared spectrum: in nujol ν max. 1733 $cm.^{-1}$ (phthalide carbonyl), in chloroform ν max. 1742 $cm.^{-1}$ (phthalide carbonyl).

The compound in ethanol gave a purple colouration with aqueous ferric chloride.

(b) A solution of ethyl 3-bromo-2-bromomethyl-6-hydroxy--4-methoxybenzoate (500 mg.) in aqueous sodium carbonate (50 c.c., 10%) was heated for 1 hour on a steam bath. The solution became yellow in colour. The cooled solution was acidified (Congo red) with concentrated hydrochloric acid, and extracted continuously with boiling chloroform for 2 hours. The chloroform extract was washed with water and dried (Na_2SO_4). Evaporation of the chloroform under reduced pressure gave a yellow solid which was crystallised from chloroform to give 4-bromo-7-hydroxy-5-methoxyphthalide (170 mg., 50%) as prisms, m.p. 236-238° (decomp.).

7-Acetoxy-4-bromo-5-methoxyphthalide. - A solution of 4-bromo-7-hydroxy-5-methoxyphthalide (700 mg.) in acetic anhydride (10 c.c.) and pyridine (1 c.c.) was heated for 2 hours on a steam bath. Water (100 c.c.) was added, and the solution warmed for a few minutes. On cooling a white crystalline precipitate separated. The crystals were filtered off, washed with water and sucked dry. Recrystallisation of the product from methanol gave 7-acetoxy-4-bromo-5-methoxyphthalide (700 mg.) as plates, m.p. 164-166°.

Found: C,44.16; H,3.26%

$C_{11}H_9O_5Br$ requires : C,43.86; H,3.01%.

Light absorption: λmax. 2190 Å. (ε = 36,700) and 2600 Å. (ε = 13,900).

Infrared spectrum: in nujol $\nu_{max.}$ 1779 cm^{-1} (acetate) and 1761 $cm.^{-1}$ (phthalide), in chloroform ν max. a broad band 1786-1767 $cm.^{-1}$ (acetate and phthalide carbonyls).

4-Bromo-5,7-dimethoxyphthalide from 4-bromo-7-hydroxy-5--methoxyphthalide. - 4-Bromo-7-hydroxy-5-methoxyphthalide (100 mg.) in solution in methanol (10 c.c.) was treated for 1 hour with excess ethereal diazomethane, when the solute in ethanol gave no colour with aqueous ferric chloride. The solvents were removed to give a gum which rapidly crystallised. Recrystallisation of the product from chloroform-methanol gave fine needles, m.p. 246-248° (Logan and Newbold[6] give m.p. 246-248°).

The m.p. was undepressed on admixture with an authentic sample of 4-bromo-5,7-dimethoxyphthalide. The infrared spectra of the two specimens in nujol were identical.

Ethyl 3-bromo-2-bromomethyl-4,6-dimethoxybenzoate. - A solution of ethyl 3-bromo-2-bromomethyl-6-hydroxy-4-methoxybenzoate (1 g.) in methanol (20 c.c.) was treated with excess ethereal diazomethane for 4 hours, when the solute in ethanol gave no colouration with aqueous ferric chloride. Evaporation of the solvents under reduced pressure gave a colourless gum which was crystallised from light petroleum (b.p. 40-60°) to give ethyl 3-bromo-2-bromomethyl-4,6-dimethoxybenzoate (880 mg.) as small prisms m.p. 98-100°.

Found: C,37.46; H,3.82%

$C_{12}H_{14}O_4Br_2$ requires: C,37.70; H,3.69%.

Light absorption: λ max. 2210 Å. (ε = 25,400) and 3080 Å. (ε = 4,100).

Infrared spectrum: in nujol ν max. 1733 $cm.^{-1}$ (ester carbonyl), in chloroform ν max. 1724 $cm.^{-1}$ (ester carbonyl).

4-Bromo-5,7-dimethoxyphthalide from ethyl 3-bromo-2-bromomethyl-4,6-dimethoxybenzoate. - To a solution of ethyl 3-bromo-2-bromomethyl-4,6-dimethoxybenzoate (500 mg.) in dioxan (20 c.c.) was added water (10 c.c.). The resulting solution was refluxed gently for 24 hours. The dioxan was distilled off under reduced pressure and the solution cooled. The white precipitate which

separated was filtered off and sucked dry. Crystallisation of the solid from chloroform-methanol gave fine needles (320 mg., 89%), m.p. 246-248° (Logan and Newbold[8] give m.p. 246-248°). The m.p. was undepressed on admixture with an authentic sample of 4-bromo-5,7-dimethoxyphthalide. The infrared spectra of the two specimens were identical.

7-Hydroxy-5-methoxyphthalide. - 4-Bromo-7-hydroxy-5--methoxyphthalide (1.5 g.) was warmed with aqueous sodium hydroxide (40 c.c., 2N) until it dissolved. The cooled solution was shaken with hydrogen at room temperature and atmospheric pressure in the presence of palladised calcium carbonate[42] (2.5 g., 2% palladium hydroxide on calcium carbonate). When absorption of hydrogen was complete, (ca. 1½ hours) the mixture was filtered, and the filtrate acidified (Congo red) with concentrated hydrochloric acid. The white solid which separated was filtered off, washed with water and sucked dry. The solid was crystallised from acetone-light petroleum (b.p. 60-80°) to give 7-hydroxy-5-methoxyphthalide (830 mg., 77%) as small prisms, m.p. 186-188°.

Found: C,60.08; H,4.66%.

$C_9H_8O_4$ requires: C,59.99; H,4.48%.

Light absorption: λ max. 2170 Å. (ε = 37,800), 2550 Å. (ε = 15,600) and 2910 Å. (ε = 4,300).

Infrared spectrum: in nujol ν max. 1733 $cm.^{-1}$ (phthalide carbonyl), in chloroform 1748 $cm.^{-1}$ (phthalide carbonyl).

The compound in ethanol gave a purple colouration with aqueous ferric chloride.

5,7-Dimethoxyphthalide from 7-hydroxy-5-methoxyphthalide.- A solution of 7-hydroxy-5-methoxyphthalide (100 mg.) in methanol (5 c.c.) was treated with excess ethereal diazomethane until the solute in ethanol gave no colouration with aqueous ferric chloride (ca. 10 mins.). The solvents were removed under reduced pressure to give a gum which rapidly crystallised. Recrystallisation of the product from chloroform-methanol gave needles, m.p. 151-153°. The m.p. was undepressed on admixture with an authentic specimen of 5,7-dimethoxyphthalide, m.p. 151-153°, prepared by Logan and Newbold.[6] The infrared spectra of the two specimens were identical.

5,7-Dimethoxyphthalide from 4-bromo-5,7-dimethoxyphthalide. (cf. Logan and Newbold, J. Chem. Soc., 1957, 1946). - A solution of 4-bromo-5,7-dimethoxyphthalide (200 mg.) in aqueous sodium hydroxide (15 c.c., 2 N) was shaken with hydrogen at room temperature and atmospheric pressure in the presence of palladised calcium carbonate[42] (400 mg., 2% palladium hydroxide on calcium carbonate). When absorption of hydrogen was complete (ca. 1 hour) the mixture was filtered, and the filtrate acidified (Congo red) with concentrated hydrochloric acid. The white solid which slowly separated was filtered off, washed with water and sucked dry. The solid was crystallised from chloroform-methanol to give 5,7-dimethoxyphthalide as needles m.p. 149-151° (Logan and

Newbold[3] give m.p. 151-153°). The m.p. was undepressed on admixture with an authentic specimen. The infrared spectra of the two specimens were identical.

Ethyl 2-Bromomethyl-6-hydroxy-4-methoxybenzoate. - Ethyl 6-hydroxy-4-methoxy-2-methylbenzoate [ethyl everninate] (2 g.) was thoroughly dried under vacuum at 60°. The material in solution in dry carbon tetrachloride (30 c.c.) in a quartz flask, heated under reflux by irradiation from a 150 w. lamp, was treated dropwise with bromine (1.53 g., 1 mol.) in dry carbon tetrachloride (10 c.c.) during 30 minutes. Each addition was made when the colour of the solution was almost discharged. Refluxing was continued for a further 15 minutes. The solvent was evaporated off under reduced pressure and the resulting yellow gum was crystallised from light petroleum (b.p. 60-80°) to give ethyl 2-bromomethyl-6-hydroxy-4-methoxybenzoate (1.7 g.) as felted needles, m.p. 92-93.5°

Found: C,45.82; H,4.68%,

$C_{11}H_{13}O_4Br$ requires: C,45.67; H,4.54%

Light absorption: λ max. 2080 Å. (ε = 11,200), 2240 Å. (ε = 17,700), 2660 Å. (ε = 7100) and 3120 Å. (ε = 4,900).

Infrared spectrum: in nujol ν max. 1650 $cm.^{-1}$ (H-bonded ester), in chloroform ν max. 1661 $cm.^{-1}$ (H-bonded ester).

The compound in ethanol gave a pale yellowish-brown colouration with aqueous ferric chloride.

Ethyl 3-bromo-6-hydroxy-4-methoxy-2-methylbenzoate. - To a solution of ethyl everninate (5.59 g.) in dry carbon tetrachloride (80 c.c.) was added methanol (0.2 c.c.). The resulting solution, heated under reflux in a quartz flask by irradiation from a 150 w. lamp, was treated dropwise with bromine (4.26 g., 1 mol.) in dry carbon tetrachloride (25 c.c.) during 30 minutes. Each addition was made when the colour of the previous addition was almost discharged. Refluxing was continued for a further 15 minutes. The solvent was evaporated off under reduced pressure and the resulting yellow gum was dissolved in light petroleum (b.p. 60-80°). Reduction of the bulk of the solvent gave crystalline material, 'A', which was filtered off. Further reduction in the volume of the solvent gave a second crystalline crop, 'B'.

The crystalline material 'A' was recrystallised from light petroleum to give ethyl 3-bromo-6-hydroxy-4-methoxy-2-methylbenzoate (3.2 g.) as fine needles, m.p. 125-127°.

Found: C,45.68; H,4.77%.

$C_{11}H_{13}O_4Br$ requires: C,45.67; H,4.54%.

Light absorption: λ max. 2180 Å. (ε = 28,300), 2620 Å. (ε = 8,900) and 3090 Å. (ε = 4,100).

Infrared spectrum: in nujol ν max. 1650 $cm.^{-1}$ (H-bonded ester), in chloroform ν max. 1655 $cm.^{-1}$ (H-bonded ester).

The compound in ethanol gave a deep purple colouration with aqueous ferric chloride.

The second crystalline crop, 'B' was recrystallised from light petroleum to give felted needles (0.6 g.) m.p. 92-93°. The m.p. of the material was undepressed on admixture with an authentic specimen of ethyl 2-bromomethyl-6-hydroxy-4-methoxybenzoate m.p. 92-93.5°. The infrared spectra of the two specimens were identical.

7-Hydroxy-5-methoxyphthalide from ethyl 2-bromomethyl-6-hydroxy-4-methoxybenzoate. - To a solution of ethyl 2-bromomethyl-6-hydroxy-4-methoxybenzoate (400 mg.) in dioxan (8 c.c.) was added water (2 c.c.) and the resulting solution refluxed gently for 24 hours. Dioxan was evaporated off under reduced pressure and the solution cooled. The white precipitate was filtered off, washed with water and sucked dry. Crystallisation of the material from acetone-light petroleum (b.p. 60-80°) gave prisms, (250 mg. 90%), m.p. 185-187°. The m.p. was undepressed with an authentic specimen of 7-hydroxy-5-methoxyphthalide m.p. 186-188°. The infrared spectra of the two specimens were identical.

Ethyl 3-bromo-4,6-dimethoxy-2-methylbenzoate. - A solution of ethyl 3-bromo-6-hydroxy-4-methoxy-2-methylbenzoate (250 mg.) in methanol (10 c.c.) was treated with excess ethereal diazomethane until the solute in ethanol gave no colouration with aqueous ferric chloride (2 hours). Removal of the solvents gave a colourless gum which was crystallised from light petroleum (b.p. 40-60°) to give ethyl 3-bromo-4,6-dimethoxy-2-methylbenzoate

(190 mg.) as prisms, m.p. 83-84.5°.

Found: C,47.28; H,4.85%

$C_{12}H_{15}O_4Br$ requires: C,47.52; H,4.99%

Light absorption: λ max. 2070 Å. (ε = 35,400) and 2880 Å. (ε = 3,300).

Infrared spectrum: in nujol ν max. 1715 cm.$^{-1}$ (ester carbonyl), in chloroform ν max. 1721 cm.$^{-1}$ (ester carbonyl).

Ethyl 3-bromo-4,6-dimethoxy-2-methylbenzoate from 3-Bromo-4,6-dimethoxy-2-methylbenzoic acid. - A solution of 3-bromo-4,6-dimethoxy-2-methylbenzoic acid.(50 mg.) in methanol (5 c.c.) was treated for 30 minutes with excess ethereal diazomethane. Evaporation of the solvents under reduced pressure gave a colourless gum which was crystallised from light petroleum (b.p. 40-60°) to give prisms, m.p. 80-82°. The compound was undepressed on admixture with a sample of ethyl 3-bromo-4,6-dimethoxy-2-methylbenzoate prepared in the preceding experiment by methylation of ethyl 3-bromo-6-hydroxy-4-methoxy-2-methylbenzoate. The two specimens had identical infrared spectra.

Ethyl 2-ethoxycarbonyl-3-methyl-4-phenyl-2-butenoate. (cf. Marion and McRae, Can. J. Res., 1940, 18, 265; and Kon and Speight, J. Chem. Soc., 1930, 775). - To powdered anhydrous zinc chloride (25 c.c.), aniline (10 c.c.) was added slowly with shaking. Diethyl malonate (80 c.c.), phenylacetone (67 g.) and acetic anhydride (60 c.c.) were added. The flask was fitted with an air condenser and calcium chloride tube and the mixture heated on a steam bath for 75 hours. The mixture was cooled, water (200 c.c.) was added and the solution extracted with ether (2 x 300 c.c.). The combined ethereal extract was washed with hydrochloric acid (8 x 200 c.c.; 4N), water and dried (Na_2SO_4). Removal of the ether gave a brown oil. The fraction of the oil which distilled at 150-185°/12 m.m. was collected. On standing overnight, crystals of acetanilide m.p. 116-117° had precipitated from the oil. The acetanilide was filtered off, the filtrate (12 g.) redistilled and the fraction boiling at 172-175°/3 m.m. was collected to give ethyl 2-ethoxycarbonyl-3-methyl-4-phenyl--2-butenoate (9 g.) as a pale yellow oil. The ester also had b.p. 142-146°/0.3 m.m.

Light absorption: λ max. 2060 Å. (ε = 19,000) and 2230 Å. (ε - 14,600).

Infrared spectrum of the oil: ν max. 1709 cm.$^{-1}$ (ester carbonyl), infrared spectrum in chloroform: ν max. 1727 cm^{-1} (ester carbonyl).

2-Carboxy-3-methyl-4-phenyl-3-butenoic acid. - Ethyl 2-ethoxycarbonyl-3-methyl-4-phenyl-2-butenoate (2 g.) was refluxed

for 2 hours with potassium hydroxide (5 g.), methanol (45 c.c.) and water (5 c.c.). Water (50 c.c.) was added, and methanol was distilled off under reduced pressure. The almost complete solution was cooled, extracted with ether (2 x 20 c.c.) and the aqueous phase acidified (Congo red) with 4N hydrochloric acid. The resulting white emulsion which slowly solidified, was extracted with ether (3 x 20 c.c.). The combined ethereal extract was washed with aqueous sodium hydrogen carbonate (3 x 20 c.c.). The combined alkaline washings were acidified (Congo red) with 4N hydrochloric acid, when a white solid separated. The solid (1.5 g.) was filtered off, washed with water and sucked dry. Crystallisation from ether-benzene gave 2-carboxy-3-methyl-4-phenyl-3-butenoic acid, m.p. 153-154° (Decomp.) as plates.

Found: C,65.48; H,5.8%; equiv., 106.

$C_{12}H_{12}O_4$ requires: C,65.45; H,5.49%; equiv., 110.1.

Light absorption: λ max. 2060 Å. (ε = 19,100) and 2470 Å. (ε = 16,200).

Infrared spectrum: in nujol ν max. 1709 $cm.^{-1}$ (carboxylic acid), in chloroform, ν max. 1724 $cm.^{-1}$ (carboxylic acid).

The compound decolourised bromine water.

3-Methyl-4-phenyl-3-butenoic acid. - 2-Carboxy-3-methyl--4-phenyl-3-butenoic acid (2 g.) was heated under atmospheric

pressure at 170-180° (bath temperature) until effervescence of carbon dioxide ceased. The residue which crystallised on cooling was recrystallised from benzene-light petroleum (b.p. 60-80°) to give 3-methyl-4-phenyl-3-butenoic acid (1.4 g.) as plates m.p. 112-114°.

Found: C,74.67; H,7.07%; equiv., 177

$C_{11}H_{12}O_2$ requires: C,74.97; H,6.86%; equiv., 176

Light absorption: λ max. 2050 Å. (ε = 18,000) and 2460 Å. (ε = 14,900).

Infrared spectrum: in nujol ν max. 1686 cm.$^{-1}$ (carboxylic acid), in chloroform ν max. 1715 cm.$^{-1}$ (carboxylic acid).

The compound decolourised bromine water and was soluble in cold aqueous sodium hydrogen carbonate.

Ethyl 2-ethoxycarbonyl-3-methyl-4-phenyl-3-butenoate. - 2-Carboxy-3-methyl-4-phenyl-3-butenoic acid (3 g.) was treated with ethereal diazoethane from nitrosoethylurea (4.5 g.). This was less than the theoretically required amount of diazoethane to prevent possible pyrazoline formation. The ethereal solution was washed with aqueous sodium hydrogen carbonate (3 x 20 c.c.), water and dried (Na_2SO_4). Removal of the ether gave ethyl 2-ethoxycarbonyl-3-methyl-4-phenyl-3-butenoate (3 g.) as a pale yellow oil b.p. 154-158°/0.3 m.m.

Light absorption: λ max. 2060 Å.(ε = 16,100) and 2470 Å.(ε = 12,700).

Infrared spectrum of the oil: ν max. 1718 cm.$^{-1}$ (ester carbonyl), infrared spectrum in chloroform: ν max. 1730 cm.$^{-1}$ (ester carbonyl).

The ester decolourised bromine water.

Hydrolysis of ethyl 2-ethoxycarbonyl-3-methyl-4-phenyl--3-butenoate to 2-carboxy-3-methyl-4-phenyl-3-butenoic acid. - Ethyl 2-ethoxycarbonyl-3-methyl-4-phenyl-3-butenoate (500 mg.), was refluxed for 2 hours with potassium hydroxide (2 g.), methanol (18 c.c.) and water (2 c.c.). Water (20 c.c.) was added and methanol distilled off under reduced pressure. The almost complete solution was washed with ether (2 x 10 c.c.), and the aqueous phase acidified with 4N hydrochloric acid. The resulting emulsion was extracted with ether (3 x 10 c.c.), and the combined ether extract was washed with water and dried (Na_2SO_4). Removal of ether gave a white solid (350 mg.) which crystallised from ether-benzene as plates m.p. 153-154° (decomp.) The m.p. was undepressed on admixture with a specimen of 2-carboxy-3-methyl-4-phenyl-3-butenoic acid. The infrared spectra of the two samples were identical.

Oxidation of 2-carboxy-3-methyl-4-phenyl-3-butenoic acid to benzaldehyde. - 2-Carboxy-3-methyl-4-phenyl-3-butenoic acid (400 mg.) was dissolved in 5% aqueous sodium carbonate (10 c.c.). The solution was heated, and to the hot solution was slowly added deci-normal aqueous potassium permanganate

(2.4 c.c.). Each addition was made when the colour of the previous addition had disappeared. Five minutes after the addition of the potassium permanganate, a few drops of methanol were added and the solution heated for a further 5 minutes. The mixture was filtered, and the filtrate cooled and extracted with chloroform (3 x 10 c.c.). The combined chloroform extract was washed with aqueous sodium hydrogen carbonate (3 x 10 c.c.) 'extract A', water and dried (Na_2SO_4). Removal of the chloroform gave a yellow oil. The oil gave a 2,4-dinitrophenylhydrazone which had m.p. 234-236°, and mixed m.p. 234-236° on admixture with benzaldehyde 2,4-dinitrophenylhydrazone.

The alkaline 'extract A' gave no precipitate on acidification with dilute hydrochloric acid.

3-Methyl-4-phenyl-3-butenoic acid and ethyl 2-ethoxycarbonyl-3-methyl-4-phenyl-3-butenoate on similar treatment with aqueous alkaline potassium permanganate gave benzaldehyde. Ethyl 2-ethoxycarbonyl-3-methyl-4-phenyl-2-butenoate and phenylacetone gave no neutral fraction but acidification of the alkaline 'extract A' gave benzoic acid m.p. 119-121° and mixed m.p. 119-121° on admixture with an authentic sample.

Ozonolysis of ethyl 2-ethoxycarbonyl-3-methyl-4-phenyl-2-butenoate to give phenylacetone. - A solution of ethyl 2-ethoxycarbonyl-3-methyl-4-phenyl-2-butenoate (1 g.) in dry chloroform (20 c.c.) was cooled in a bath of acetone-solid carbon

dioxide. Ozone was passed slowly through the solution until it ceased to be taken up immediately. Removal of the chloroform under reduced pressure gave a yellow oil. The oil gave a 2,4-dinitrophenylhydrazone m.p. 153-155° and mixed m.p. 153-155° on admixture with a sample of phenylacetone 2,4-dinitrophenylhydrazone.

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PART II

Isomerisation of a Homophthalic Acid Derivative.

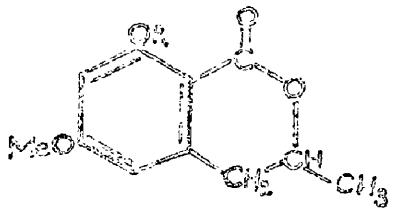
SUMMARY

In the course of investigation of a possible synthetic route to (±)-3,5-dihydro-8-hydroxy-6-methoxy-3-methylisocoumarin, some novel rearrangements of homophthalic acid derivatives were discovered. In one case 3-benzyloxy-2-ethoxycarbonyl-5--methoxyphenylacetic acid was converted into ethyl 3-benzyloxy--2-carboxy-5-methoxyphenylacetate by anhydrous acidic reagents. The reverse rearrangement was effected by aqueous alkali. Mechanisms for the rearrangements are discussed.

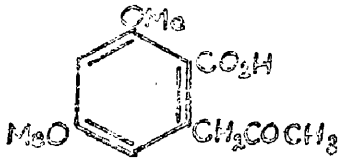
During preparation of 3-benzyloxy-2-ethoxycarbonyl-5--methoxyphenylacetic acid, a small amount of an isomeric acid was, on occasion, also obtained. The reactions of this acid suggested that it was a geometric isomer of 3-benzyloxy-2-ethoxycarbonyl-5-methoxyphenylacetic acid. Possible structures of two geometric isomers of 3-benzyloxy-2-ethoxycarbonyl-5--methoxyphenylacetic acid are discussed.

INTRODUCTION

Sondheimer[1] isolated a colourless optically active crystalline substance from the hexane extract of bitter carrots. By analytical and degradative studies, he showed this substance to be (-)-3,4-dihydro-8-hydroxy-6-methoxy-3-methyl-isocoumarin (I, R = H). Logan and Newbold[2] confirmed this structure by synthesis of (±)-3,4-dihydro-6,8-dimethoxy-3-methyl-isocoumarin (I, R = Me) which they found to be identical with the racemic methyl ether of the carrot compound.



(I)

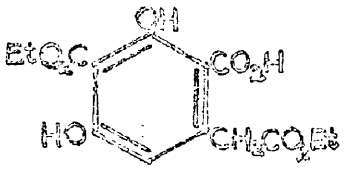


(II)

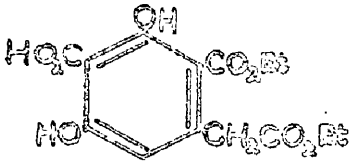
The starting material for Logan and Newbold's synthesis was 2-carboxy-3,5-dimethoxybenzyl methyl ketone (II), treatment of which with sodium borohydride gave (I, R = Me). The preparation of the starting material (II) is described by Nogami[3].

The first step in the preparation of (II) is the condensation of two molecules of ethyl acetone dicarboxylate (III) in the presence of ethyl chloroacetate and magnesium to give ethyl 4-carboxy-2-ethoxycarbonyl-3,5-dihydroxyphenylacetate (V). A small amount of magnesium catalyses the reaction, but a

relatively large amount of ethyl chloroacetate is required, apparently to activate the magnesium. This condensation was first described by Jerdan,[4] who formulated the condensation product as (IV), but later work by Asahina and Nogami[5] proved the structure to be in fact (V).

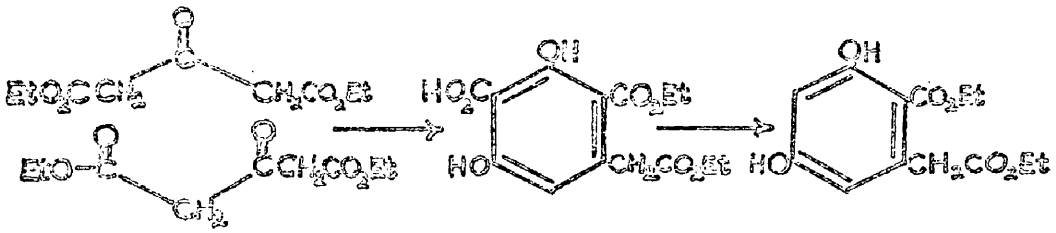


(IV)

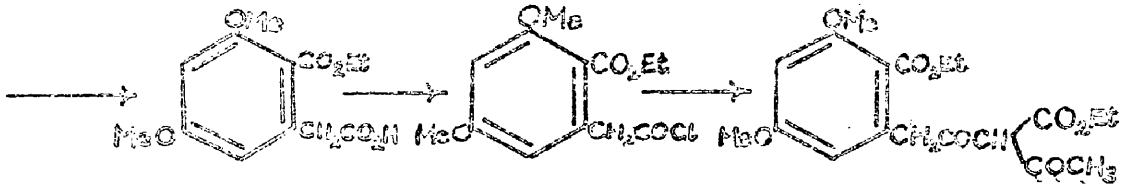


(V)

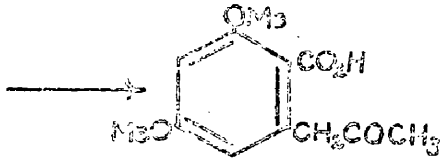
Decarboxylation of (V) to ethyl 2-ethoxycarbonyl-3,5-dihydroxyphenylacetate (VI) was affected by heating with copper powder and quinoline. Methylation of (VI) with methyl iodide, followed by alkaline hydrolysis gave 2-ethoxycarbonyl-3,5--dimethoxyphenylacetic acid (VII). Treatment of (VII) with phosphorus trichloride in chloroform at room temperature for 24 hours gave 2-ethoxycarbonyl-3,5-dimethoxyphenylacetyl chloride (VIII), which was condensed with the sodio derivative of ethyl acetoacetate to give (IX). On treatment of (IX) with alkali the ketone (II) was obtained. It should be noted that 'Chemical Abstracts'[6] are in error in the details which they give for the preparation of (II).



(III) (V) (VI)

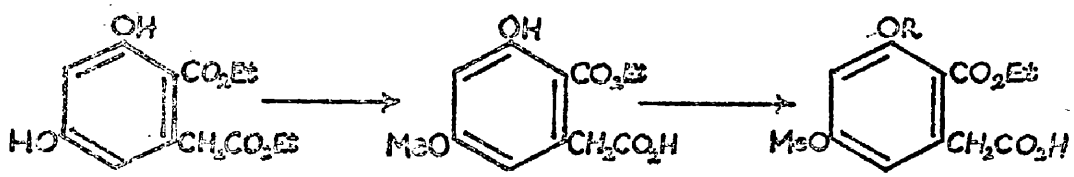


(VII) (VIII) (IX)



(II)

It was decided to attempt a synthesis of the racemic carrot compound itself (±)-3,4-dihydro-8-hydroxy-6-methoxy-3--methylisocoumarin (I, R = H) by a similar route. Ethyl 2-ethoxycarbonyl-3,5-dihydroxyphenylacetate (VI) can be selectively methylated by diazomethane, and subsequent alkaline hydrolysis will give 2-ethoxycarbonyl-3-hydroxy-5-methoxy-phenylacetic acid (X). Protection of the 3-hydroxyl group in (X)



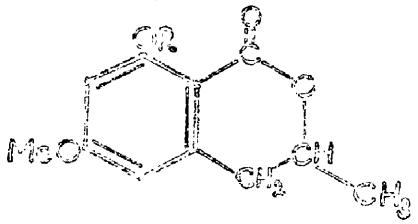
(VI) (X) (XI)

by a readily removable group such as an acetyl or benzyl group would give (XI, R = Ac or Bz). A series of reactions starting from (XI), parallel to those described above for the dimethoxy series, and final removal of the acetyl group by alkaline hydrolysis, or the benzyl group by hydrogenolysis, would give (±)-3,4-dihydro-8-hydroxy-6-methoxy-3-methylisocoumarin (I, R = H).

Several of the proposed reactions were in fact carried out, but it was found that synthesis of (I, R = H) by this route was impracticable. As a result of this work however, other topics of interest were found concerning the intermediates in the proposed synthesis. The crowding in the 1,2,3-tri-substituted system of the compounds in this series, and the proximity of the benzoic carboxyl and the phenylacetic carboxyl functions, as shown by molecular models, together give rise to some unusual reactions. In 3-benzyloxy-2-ethoxycarbonyl-5--methoxyphenylacetic acid (XI, R = Benzyl), due to the size of the benzyl group, there is extreme steric crowding. It is with the reactions of this compound and of its derivatives that this work is chiefly concerned.

THEORETICAL

The compound obtained by Sondheimer[1] from the hexane extract of bitter carrots, has been shown by him to be almost certainly (-)-3,4-dihydro-8-hydroxy-6-methoxy-3-methyliso coumarin (I, R = H). Logan and Newbold's[2] synthesis of the racemic methyl ether (I, R = Me) of the carrot compound confirmed this structure. The route by which they synthesised (±)-3,4-dihydro-6,8-dimethoxy-3-methylisocoumarin (I, R = Me) is described in the Introduction. It seemed to us a simple matter



(I)

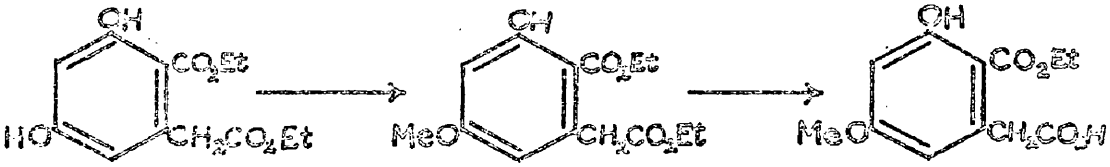
by a parallel series of reactions, starting from 2-ethoxycarbonyl--3-hydroxy-5-methoxyphenylacetic acid (X) to synthesise the racemic carrot compound (I, R = H) itself. The 3-hydroxyl group would be protected by a readily removable group such as an acetyl or benzyl group. Subsequent removal of the acetyl group by alkaline hydrolysis, or of the benzyl group by hydrogenolysis would give (I, R = H) [see Introduction].

Selective methylation of ethyl 2-ethoxycarbonyl-3,5--dihydroxyphenylacetate (VI) by brief treatment with diazomethane gave ethyl 2-ethoxycarbonyl-3-hydroxy-5-methoxyphenylacetate (XII). The 3-hydroxyl groups of other compounds in this series (X), (XII),

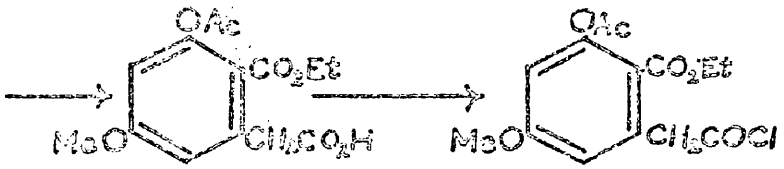
(XV), (XXI), (XXIV) and (XXV) were similarly resistant to methylation, a 24 hour treatment with excess ethereal diazomethane giving only partial methylation of that group. The inactivity of the 3-hydroxyl group is due to intramolecular hydrogen bonding of that group with the adjacent ester carbonyl group.

Mild alkaline hydrolysis of (XII) gave 2-ethoxycarbonyl--3-hydroxy-5-methoxyphenylacetic acid (X). It was noted that (X) was unaffected even on prolonged vigorous alkaline hydrolysis treatment. The 2-ethoxycarbonyl group of all benzoic ester compounds examined in the course of this work proved to be equally inert to vigorous alkaline hydrolysis conditions. Not hydrogen bonding, but steric deactivation confers this stability since most of these compounds have the adjacent 3-hydroxyl group protected.

Acetylation of (X) by acetic anhydride and pyridine gave 3-acetoxy-2-ethoxycarbonyl-5-methoxyphenylacetic acid (XIII). We were now in a position to elaborate the phenylacetic side chain as in the dimethoxy series. Treatment of (XIII) with thionyl chloride gave the crude acid chloride (XIV) as a brown uncrystallisable gum. During the subsequent condensation of (XIV) with the sodio derivative of ethyl acetoacetate, followed by alkaline hydrolysis, decomposition took place and a brown amorphous powder only was obtained.

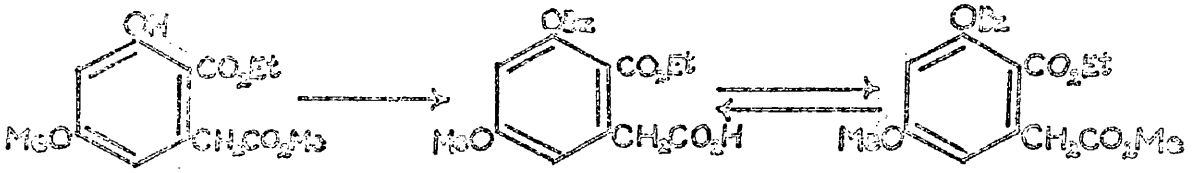


(VI) (XII) (X)



(XIII) (XIV)

In view of the probable greater stability of the benzyl ether, it was decided to attempt elaboration of the phenylacetic side chain of 3-benzyloxy-2-ethoxycarbonyl-5-methoxyphenylacetic acid (XVI). Brief treatment of 2-ethoxycarbonyl-3-hydroxy-5-methoxyphenylacetic acid (X) with diazomethane gave methyl 2-ethoxycarbonyl-3-hydroxy-5-methoxyphenylacetate (XV). Benzylation of (XV) followed by alkaline hydrolysis under the usual conditions for hydrolysis of a phenylacetic ester gave (XVI). This preparation employed benzylation of (XV) rather than (XII) since the former is more readily purified. The acid (XVI) was characterised as its methyl ester methyl 3-benzyloxy-2-ethoxycarbonyl-5-methoxyphenylacetate (XVII). The methyl ester (XVII) returned the acid (XVI) on mild alkaline hydrolysis.



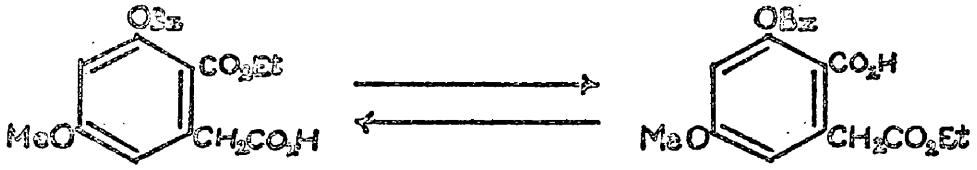
(XV) (XVI) (XVII)

3-Benzyloxy-2-ethoxycarbonyl-5-methoxyphenylacetic acid (XVI) was treated with the usual acid chloride forming reagents, phosphorus trichloride in dry ethanol free chloroform at room temperature, and thionyl chloride at reflux. Both treatments gave the same crystalline product in 75% yield in the former and 55% yield in the latter case. The material, which was recrystallised from anhydrous solvents had m.p. 116-117°. The compound was not an acid chloride, but a carboxylic acid, and did not contain chlorine. By analysis this compound was isomeric with (XVI). Titration indicated it to be a carboxylic acid having the same Equivalent as (XVI). Neither (XVI) nor the acid m.p. 116-117° in solution in ethanol gave a colour with aqueous ferric chloride. The m.p. of this compound was depressed on admixture with (XVI), and their infrared spectra were different. Thus (XVI) and the acid m.p.116-117° were different compounds not crystalline modifications of (XVI). The acid m.p. 116-117° gave a crystalline methyl ester isomeric with methyl 3-benzyloxy-2-ethoxycarbonyl-5-methoxyphenylacetate (XVII). The two methyl esters had different m.p., and depressed

on mixed m.p. Their infrared spectra were also different. Treatment of the acid m.p. 116-117° with aqueous, aqueous ethanolic or aqueous methanolic alkali returned 3-benzyloxy-2-ethoxycarbonyl-5-methoxyphenylacetic acid (XVI) in good yield. The acid m.p. 116-117° was, however, stable in cold $N/_{100}$ sodium hydroxide and was recovered unchanged on acidification of the solution.

Structure of the Acid m.p. 116-117°.

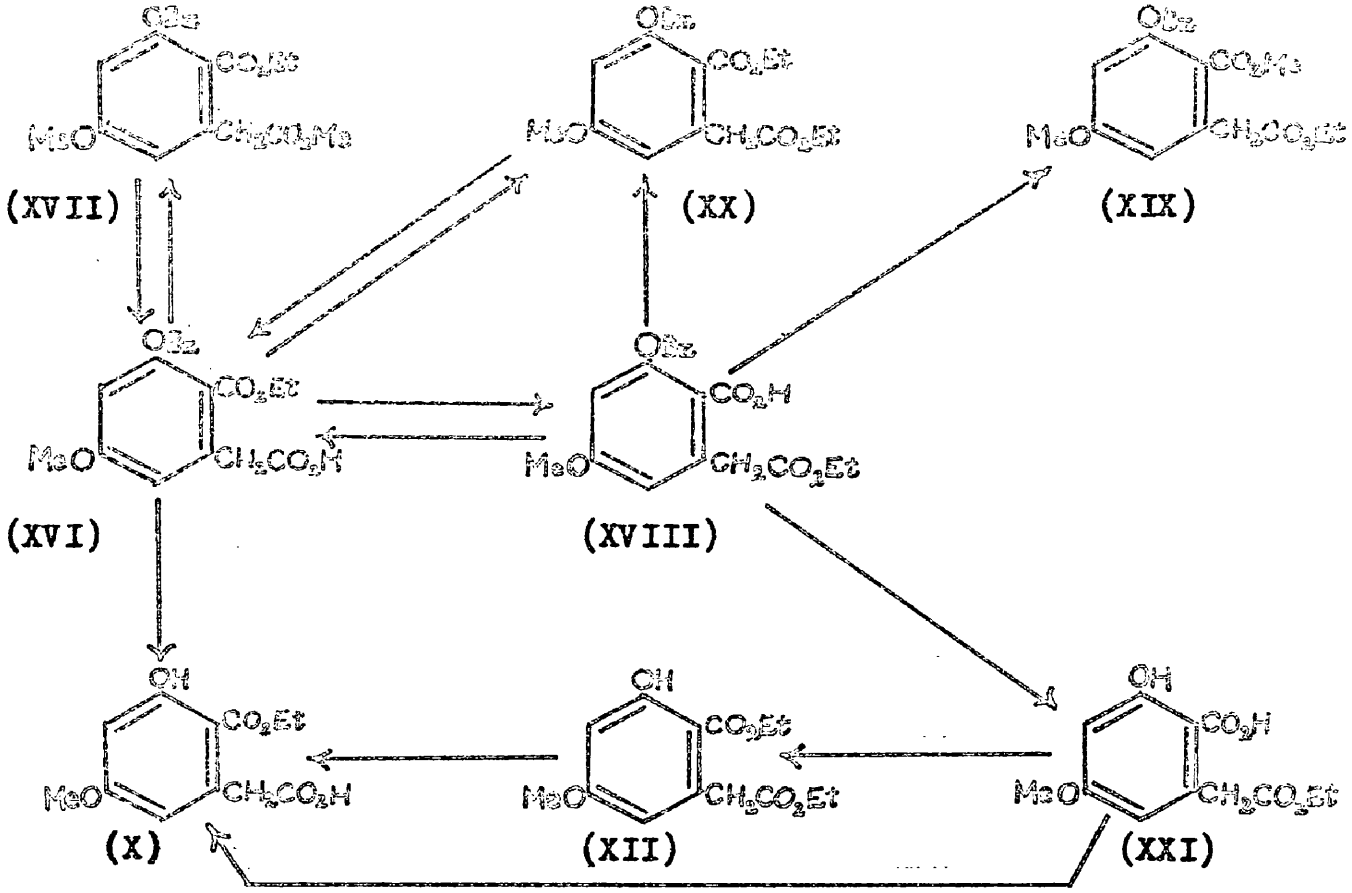
3-Benzyloxy-2-ethoxycarbonyl-5-methoxyphenylacetic acid (XVI) and the acid m.p. 116-117° were esterified with diazoethane. Both ethyl esters were oils, but comparison of their infrared spectra indicated them to be identical. Mild alkaline hydrolysis of both esters gave (XVI). Clearly then, conversion of (XVI) to the acid m.p. 116-117° and vice versa, involved an interchange of the acid and ester functions. The acid m.p. 116-117° was tentatively formulated as ethyl 3-benzyloxy-2-carboxy-5-methoxyphenylacetate (XVIII).



(XVI) (XVIII)

Further evidence was sought to prove that the acid m.p. 116-117° was ethyl 3-benzyloxy-2-carboxy-5-methoxyphenyl

acetate (XVIII). 3-Benzyloxy-2-ethoxycarbonyl-5-methoxyphenyl-acetic acid (XVI) was first of all debenzylated to ascertain that we were indeed dealing with a compound of that structure. Hydrogenation of (XVI) at atmospheric pressure in the presence of palladised charcoal catalyst and magnesium oxide gave a phenolic product identical with 2-ethoxycarbonyl-3-hydroxy-5-methoxyphenyl-acetic acid (X). Thus structure (XVI) is confirmed. Debenzylation



of the acid m.p. 116-117° (XVIII) gave a salicylic acid derivative which was isomeric with 2-ethoxycarbonyl-3-hydroxy-5-methoxyphenyl-acetic acid (X). Esterification of the salicylic acid derivative

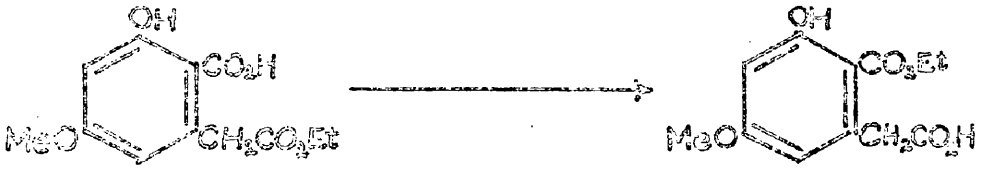
with diazoethane gave a phenolic ester 'A', which on alkaline hydrolysis gave a carboxylic acid 'B'. 'A' was identical with ethyl 2-ethoxycarbonyl-3-hydroxy-5-methoxyphenylacetate (XII), and 'B' was identical with 2-ethoxycarbonyl-3-hydroxy-5-methoxyphenylacetic acid (X). The salicylic acid derivative was therefore formulated as ethyl 2-carboxy-3-hydroxy-5-methoxyphenylacetate (XXI).

It now seemed fairly certain that the acid m.p. 116-117°, isomeric with (XVI) was ethyl 3-benzyloxy-2-carboxy-5-methoxyphenylacetate (XVIII), and that (XVI) and (XVIII) can be readily interconverted in good yield. Phosphorus trichloride in chloroform or thionyl chloride cause the isomerisation of (XVI) to (XVIII). It was found that dry hydrogen chloride in chloroform also brought about the isomerisation to give (XVIII) in 20% yield, the balance being recovered as starting material (XVI). Hydrogen chloride in alcohols or aqueous alcohols, however, did not cause isomerisation.

A structure can now be assigned to the methyl ester of the acid m.p. 116-117°. It is ethyl 3-benzyloxy-5-methoxy-2-methoxycarbonylphenylacetate (XIX). The common ethyl ester of (XVI) and XVIII) is ethyl 3-benzyloxy-2-ethoxycarbonyl-5-methoxyphenylacetate (XX).

The action of mild alkaline hydrolysis of ethyl 2-carboxy-

-3-hydroxy-5-methoxyphenylacetate (XXI) was examined. The product was not the expected diacid, but 2-ethoxycarbonyl-3--hydroxy-5-methoxyphenylacetic acid (X). Thus (XXI) on mild alkaline hydrolysis undergoes rearrangement analogous to the conversion of (XVIII) to (XVI). Treatment of (X) with phosphorus



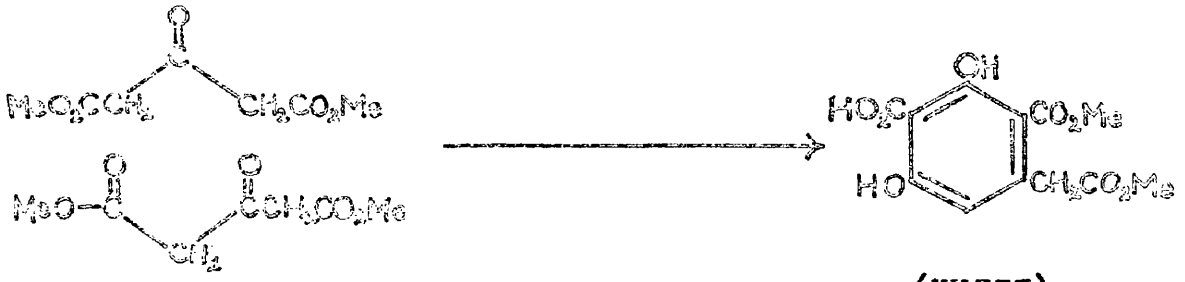
(XXI) (X)

trichloride in chloroform and with dry hydrogen chloride in chloroform failed, however, to bring about the reverse reaction analogous to conversion of (XVI) to (XVIII).

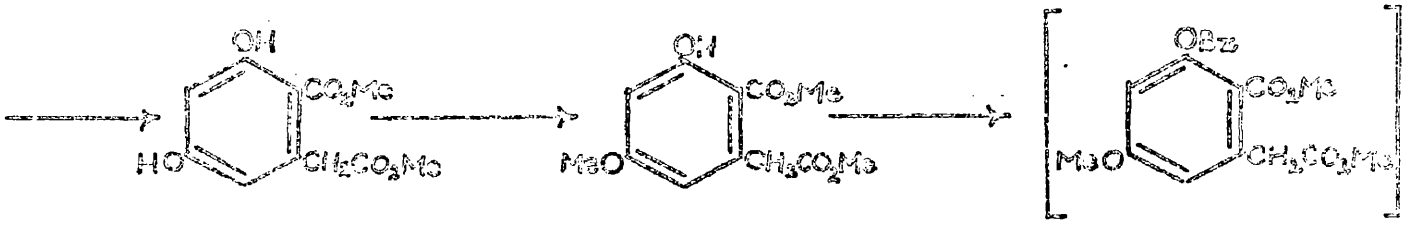
Due to the unique nature of the isomerisation of 3-benzyloxy-2-ethoxycarbonyl-5-methoxyphenylacetic acid (XVI) and ethyl 3-benzyloxy-2-carboxy-5-methoxyphenylacetate (XVIII), synthetic confirmation of the structure (XVIII) was required. 3-Benzyloxy--5-methoxy-2-methoxycarbonylphenylacetic acid (XXVI) and its ethyl ester ethyl 3-benzyloxy-5-methoxy-2-methoxycarbonylphenylacetate (XIX) were therefore synthesised by an unambiguous route.

Condensation of two molecules of methyl acetone dicarboxylate (XXII) in the presence of magnesium powder and ethyl chloroacetate gave methyl 4-carboxy-3,5-dihydroxy-2-methoxycarbonylphenylacetate (XXIII), which was decarboxylated in the presence of copper powder and quinoline to methyl 3,5-dihydroxy-2-methoxycarbonylphenyl-

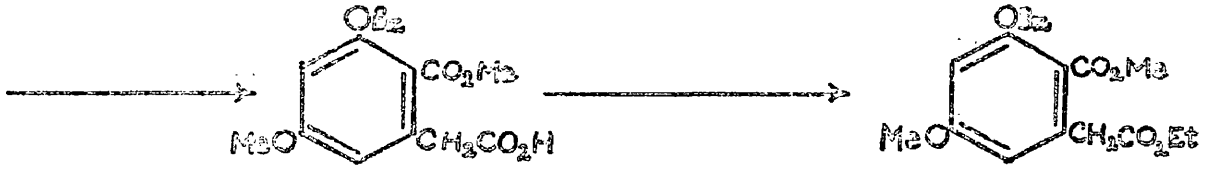
acetate (XXIV). By brief treatment with diazomethane, (XXIV) was selectively methylated to give methyl 3-hydroxy-5-methoxy-2-methoxycarbonylphenylacetate (XXV). Benzylation of (XXV)followed



(XXII) (XXIII)



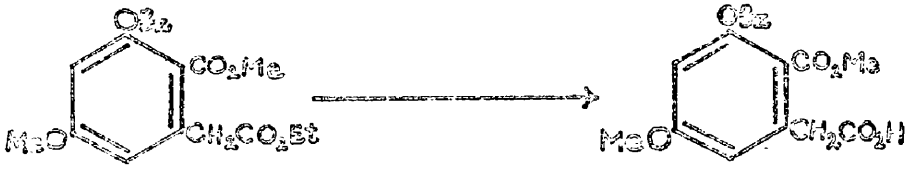
(XXIV) (XXV)



(XXVI) (XIX)

by mild alkaline hydrolysis gave 3-benzyloxy-5-methoxy-2-methoxy-carbonylphenylacetic acid (XXVI). On treatment of (XXVI) with ethereal diazoethane, ethyl 3-benzyloxy-5-methoxy-2-methoxycarbonyl-phenylacetate (XIX) was obtained, and was found to be identical with the methyl ester of the acid m.p. 116-117°. The methyl ester (XIX) of the acid m.p. 116-117° on mild alkaline hydrolysis gave a carboxylic acid which was identical with 3-benzyloxy-5-methoxy-2--methoxycarbonylphenylacetic acid (XXVI) synthesised above, thus

providing further confirmation. Structure (XVIII) can now be positively assigned to the acidic product m.p. 116-117° from the isomerisation of 3-benzyloxy-2-ethoxycarbonyl-5-methoxyphenyl-acetic acid (XVI).



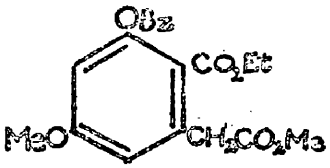
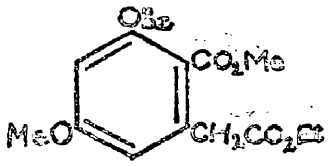
(XIX) (XXVI)

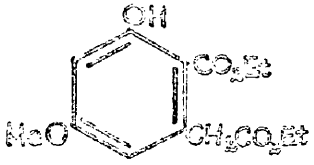
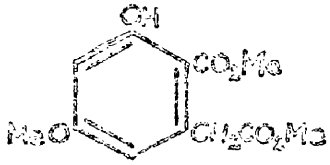
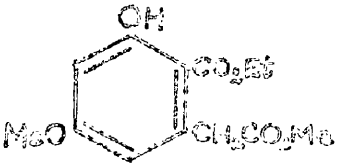
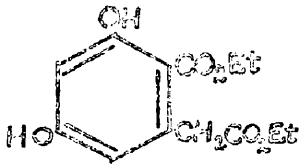
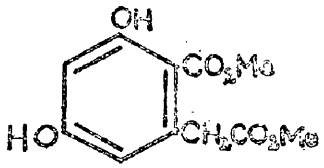
Infrared Absorption of Homophthalic Acid Derivatives.

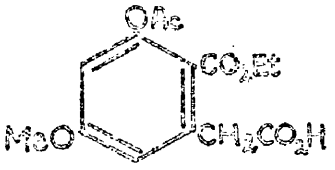
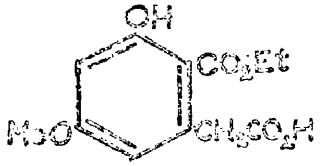
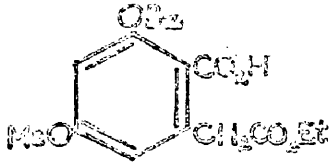
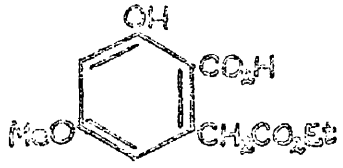
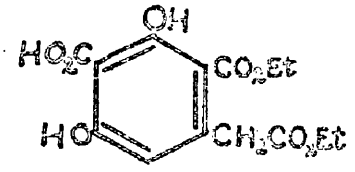
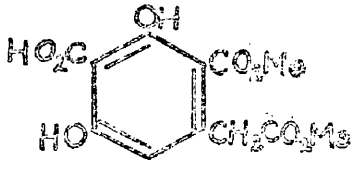
Assignments have been made for bands in the carbonyl regions of all compounds prepared during this work [TableI]. These compounds are derivatives of homophthalic acid and may be divided into three classes: diesters, phenylacetic acid-benzoic esters and phenylacetic ester-benzoic acids. Each group is discussed separately.

TABLE I.

(All values in cm.$^{-1}$)

	Nujol	Chloroform
 (XVII)	1748 (phenylacetic ester) 1715 (benzoic ester)	1736 (phenylacetic ester)
 (XIX)	1736 (phenylacetic ester) 1712 (benzoic ester)	1733 (phenylacetic ester)

	Nujol	Chloroform
 (XII)	1733 (phenylacetic ester) 1653 (H-bonded benzoic ester)	1736 (phenylacetic ester) 1661 (H-bonded benzoic ester)
 (XXV)	1739 (phenylacetic ester) 1661 (H-bonded benzoic ester)	1739 (phenylacetic ester) 1667 (H-bonded benzoic ester)
 (XV)	1739 (phenylacetic ester) 1653 (H-bonded benzoic ester)	1739 (phenylacetic ester) 1658 (H-bonded benzoic ester)
 (VI)	1712 (phenylacetic ester lowered by strong intermolecular H-bonding) 1664 (H-bonded benzoic ester)	1736 (phenylacetic ester) 1661 (H-bonded benzoic ester)
 (XXIV)	1706 (phenylacetic ester lowered by strong intermolecular H-bonding) 1653 (H-bonded benzoic ester)	1736 (phenylacetic ester) 1667 (H-bonded benzoic ester)
 (XVI)	1724 (benzoic ester) 1681 (phenylacetic acid dimer)	1724 (benzoic ester)
 (XXVI)	1727 (benzoic ester)	1724 (benzoic ester)

	Nujol	Chloroform
 (XIII)	1757 (acetate). 1718 (benzoic ester).	1767 (acetate). 1721 (benzoic ester).
 (X)	1700 (phenylacetic acid dimer). 1667 (H-bonded benzoic ester).	1718 (phenylacetic acid monomer). 1661 (H-bonded benzoic ester).
 (XVIII)	1736 (phenylacetic ester). 1684 (benzoic acid dimer).	1736 (phenylacetic ester).
 (XXI)	1736 (phenylacetic ester).	1736 (phenylacetic ester). 1656 (H-bonded benzoic acid).
 (V)	1742 (phenylacetic ester). 1692 (H-bonded benzoic ester). 1645 (H-bonded benzoic acid).	1739 (phenylacetic ester). 1698 (H-bonded benzoic ester). 1647 (H-bonded benzoic acid).
 (XXIII)	1742 (phenylacetic ester). 1692 (H-bonded benzoic ester)	1742 (phenylacetic ester) 1697 (H-bonded benzoic ester). 1656 (H-bonded benzoic acid)

Homophthalic Acid Diesters

Compounds of this type are (XVII), (XIX), (XII), (XXV), (XV), (VI) and (XXIV). Two carbonyl bands may be present in their spectra, one due to the benzoic ester and the other due to the phenylacetic ester group. Benzoic esters[7,13-18] have been found to absorb in the range 1730-1717 cm.$^{-1}$. The phenylacetic ester group will behave as a normal saturated ester[7,13-18] the bands of which are usually in the range 1750-1735 cm.$^{-1}$. In nujol, (XVII) exhibits a band at 1748 cm.$^{-1}$ due to the phenylacetic ester group, and a band at 1715 cm.$^{-1}$ due to the benzoic ester group. In chloroform, the phenylacetic ester band is at 1736 cm.$^{-1}$ while the benzoic ester band disappears. In nujol (XIX) shows the phenylacetic ester band at 1736 cm.$^{-1}$ and the benzoic ester band at 1712 cm.$^{-1}$. In chloroform the phenylacetic ester band is at 1733 cm.$^{-1}$ while the benzoic ester band again disappears. Of the remaining diesters, (XII), (XXV), (XV), (VI) and (XXIV), all have a free phenolic hydroxyl group adjacent to the benzoic ester group. The benzoic ester groups show absorption at lowered frequencies, 1664-1653 cm.$^{-1}$ in nujol, and 1667-1658 cm.$^{-1}$ in chloroform, due to chelation with the phenolic hydroxyl group.[9] All show phenylacetic ester bands in the range 1739-1733 cm.$^{-1}$ in chloroform. In nujol, the phenylacetic ester frequencies of the two dihydroxydiesters (VI) and (XXIV) are considerably lowered, clearly because of greater intermolecular hydrogen bonding with the two free hydroxyl groups.

Phenylacetic Acid-Benzoic Esters.

Compounds of this type are (XVI), (XXVI), (XIII) and (X). These compounds may show two bands, one due to the benzoic ester group, the other due to the phenylacetic acid group. The phenylacetic acid group will behave as a normal saturated aliphatic acid,[7,8,15,19] the bands of which are usually within the range 1725-1705 cm^{-1}. The bands of (XVI), (XXVI) and (XIII) require no comment except that the phenylacetic acid band of (XVI) in nujol at 1681 $cm.^{-1}$ is much lower than would be predicted. In (X) the benzoic ester frequency is lowered by intramolecular hydrogen bonding with the 3-hydroxyl group.

Phenylacetic Ester-Benzoic Acids.

Compounds of this type are (XVIII) and (XXI). In nujol and chloroform, both show the usual phenylacetic ester band. An aryl acid dimer[7,8,15,19] shows absorption in the region of 1685 $cm.^{-1}$ In nujol, (XVIII) shows a band at 1684 $cm.^{-1}$ due to the benzoic acid dimer. This band, however, disappears in chloroform. In chloroform, (XXI) shows a band at 1656 $cm.^{-1}$, a typical value for a hydrogen bonded benzoic acid.[10]

The two remaining compounds (V) and (XXIII) require comment. Both show the usual phenylacetic ester band in nujol and chloroform. Each also shows a band in the 1650 $cm.^{-1}$ region, and another in the 1690 $cm.^{-1}$ region. In nujol, the band at 1692 $cm.^{-1}$ is too high to be ascribed to a benzoic acid dimer,

and much too high to be due to a hydrogen bonded benzoic acid. Clearly then the band in the 1650 cm.$^{-1}$ region in (V) and (XXIII) must be assigned to the hydrogen bonded benzoic acid,[10] and the band in the 1690 cm.$^{-1}$ region is due to the intramolecularly hydrogen bonded benzoic ester. This value for a chelated benzoic ester is high, but is due to the nature of the hydrogen bond. Both phenolic hydroxyl groups may enter into hydrogen bonding with the 4-carboxyl group. The tendency of the 3-hydroxyl group to form a bond with the benzoic ester carbonyl will thus be lessened, hence the relatively weak nature of the intramolecular hydrogen bond with the benzoic ester, and the relatively high carbonyl stretching frequency of the hydrogen bonded benzoic ester.

Table II lists the carbonyl frequency ranges, excluding the anomalous cases described above, for the six types of carbonyl function considered.

TABLE II.

	Nujol	Chloroform
Phenylacetic ester.	1748-1733 cm.$^{-1}$	1742-1733 cm.$^{-1}$
Benzoic ester.	1727-1712 cm.$^{-1}$	1724-1721 cm.$^{-1}$
Intramolecularly hydrogen bonded benzoic ester.	1667-1653 cm.$^{-1}$	1667-1658 cm.$^{-1}$
Phenylacetic acid	1700, 1681 cm.$^{-1}$	1718 cm.$^{-1}$
Benzoic acid.	1684 cm.$^{-1}$	-
Intramolecularly hydrogen bonded benzoic acid	1645 cm.$^{-1}$	1647-1656 cm.$^{-1}$

The Anhydride of Ethyl 3-Benzyloxy-2-carboxy-5-methoxyphenylacetate.

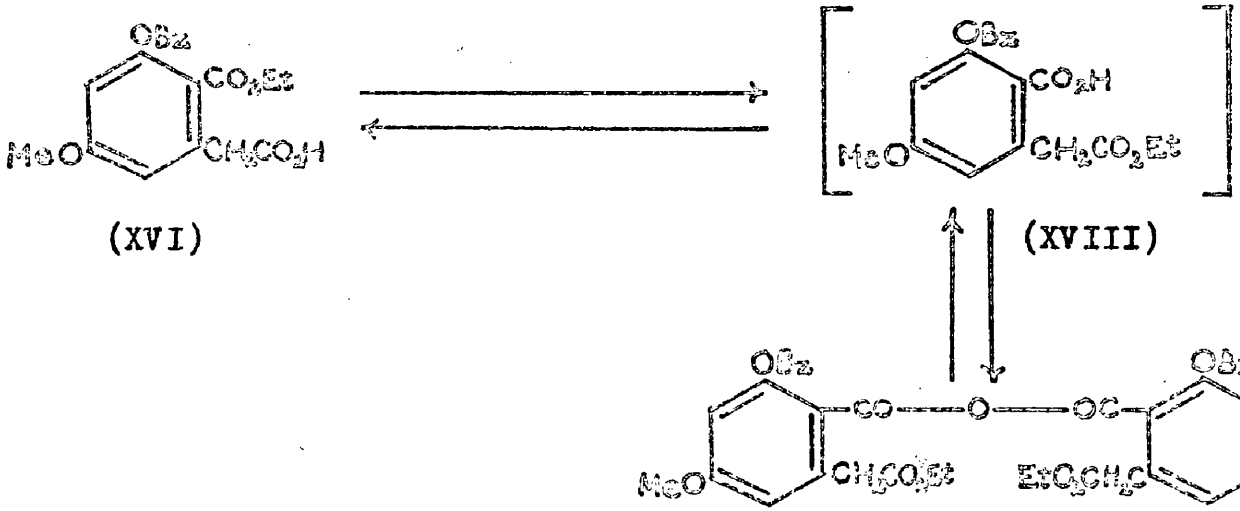
More vigorous treatment of 3-benzyloxy-2-ethoxycarbonyl--5-methoxyphenylacetic acid (XVI) with phosphorus trichloride was investigated in the hope that we might thus obtain the acid chloride. A solution of (XVI) in the usual quantities of phosphorus trichloride and chloroform was refluxed for a short time. The product, which was crystallised from anhydrous solvents had m.p. 170-173°. The product was not an acid chloride and did not contain chlorine. It was not a carboxylic acid since it did not dissolve in cold aqueous sodium hydrogen carbonate, and was soluble in 5% aqueous sodium hydroxide only on warming. It gave no colour with aqueous ferric chloride. Analyses of this compound were unsatisfactory, but suggested that it was an anhydride. Its Molecular Weight, determined by the Rast method, was approximately double the Molecular Weight of (XVI) and (XVIII) The compound was unstable, and after two days exposure to the atmosphere, the m.p. of an analytically pure sample had dropped to 155-162°. Mild alkaline hydrolysis of the compound m.p. 170-173° gave 3-benzyloxy-2-ethoxycarbonyl-5-methoxyphenylacetic acid (XVI). The compound showed infrared bands in chloroform at 1796 $cm.^{-1}$ (anhydride), 1750 $cm.^{-1}$ (phenylacetic ester) and 1097 $cm.^{-1}$ (anhydride) and an inflexion at 1727 $cm.^{-1}$, and in nujol, maxima at 1789 $cm.^{-1}$ (anhydride), 1751 $cm.^{-1}$ (phenylacetic ester) and 1099 $cm.^{-1}$ (anhydride) and an inflexion at 1730 $cm.^{-1}$.

Randall et al.[20] have observed that the two carbonyl absorption bands of an anhydride are usually approximately 60 cm.$^{-1}$ apart, and that this is a useful pointer in their identification. In the spectrum of the compound m.p. 170-173°, the band at 1796 cm.$^{-1}$ and the inflexion at 1727 cm.$^{-1}$ in chloroform are 69 cm.$^{-1}$ apart. In nujol, the band at 1789 cm.$^{-1}$ and the inflexion at 1730 cm.$^{-1}$ are 59 cm.$^{-1}$ apart. Thus the compound m.p. 170-173° is the anhydride of either 3-benzyloxy-2-ethoxycarbonyl-5-methoxyphenylacetic acid (XVI) or ethyl 3-benzyloxy-2-carboxy-5-methoxyphenylacetate (XVIII).

The band at 1750 cm.$^{-1}$ in chloroform and at 1751 cm.$^{-1}$ in nujol indicates the compound to be a phenylacetic ester, and therefore to be a benzoic anhydride. Phenylacetic anhydride[11] shows bands at 1808 cm.$^{-1}$ and 1745 cm.$^{-1}$, and aliphatic anhydride generally, show bands at even higher frequencies,[11,12] while benzoic anhydride[12] shows bands at 1789 cm.$^{-1}$ and 1727 cm^{-1}. The compound m.p. 170-173° is thus indicated to be a benzoic anhydride possessing a phenylacetic ester function, it was therefore formulated as the anhydride of ethyl 3-benzyloxy-2-carboxy-5-methoxyphenylacetate, (XXVII).

Similar treatment of (XVIII) with phosphorus trichloride in chloroform gave the compound m.p. 170-173°. Conversion of (XVIII) to (XVI) by phosphorus trichloride for subsequent formation of the anhydride of (XVI) is impossible. Thus, by this evidence,

the compound is also indicated to be the anhydride (XXVII) of ethyl 3-benzyloxy-2-carboxy-5-methoxyphenylacetate (XVIII).



(XVI) (XVIII)

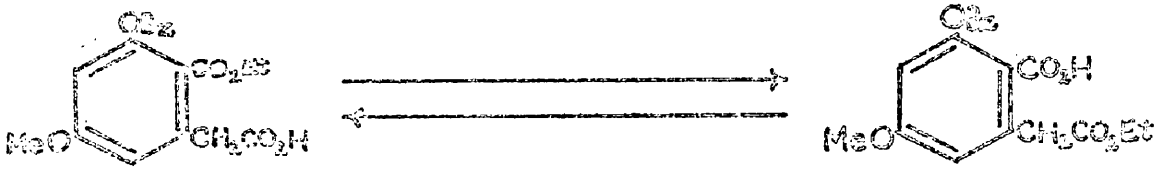
(XXVII)

The formulation (XXVII) is in agreement with the conditions of formation of the anhydride. The more vigorous phosphorus trichloride treatment of 3-benzyloxy-2-ethoxycarbonyl--5-methoxyphenylacetic acid (XVI) first of all isomerised it to ethyl 3-benzyloxy-2-carboxy-5-methoxyphenylacetate (XVIII). Dehydration of (XVIII) then gave the anhydride (XXVII). During the reverse reaction, treatment of the anhydride (XXVII) with alkali regenerated the acid (XVIII), which was immediately isomerised by the alkali to give (XVI) as usual.

Mechanism of Isomerisation.

3-Benzyloxy-2-ethoxycarbonyl-5-methoxyphenylacetic acid (XVI) is isomerised to ethyl 3-benzyloxy-2-carboxy-5-methoxyphenyl-

acetate (XVIII) by the action of acidic reagents under anhydrous conditions. The reverse change (XVIII) to (XVI) is brought about by aqueous alkaline reagents. Ethyl 2-carboxy-3-hydroxy--5-methoxyphenylacetate (XXI) has been similarly isomerised to 2-ethoxycarbonyl-3-hydroxy-5-methoxyphenylacetic acid (X), but anhydrous acidic reagents do not effect the reverse rearrangement.



(XVI) (XVIII)

(X) (XXI)

Base catalysed and acid catalysed (sodium alkoxides and sulphonic acids) intermolecular ester interchange is known, although the mechanism by which it takes place has not been discussed.[21] For example, ethyl acetate and methyl propionate form an equilibrium mixture containing the original esters with

$$CH_3CO_2Et + CH_3CH_2CO_2Me \rightleftharpoons CH_3CO_2Me + CH_3CH_2CO_2Et$$

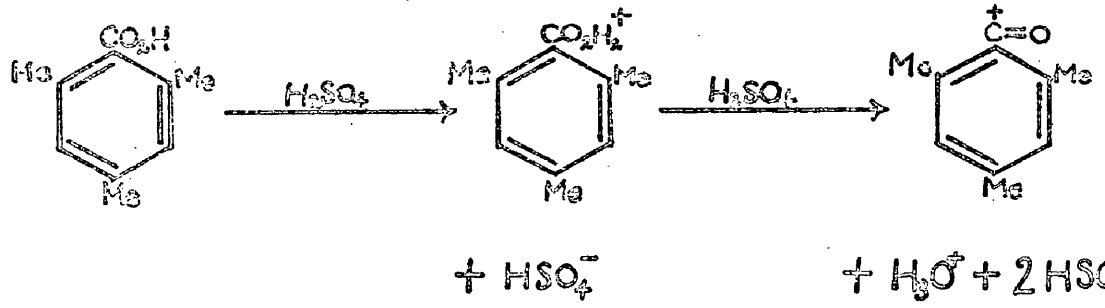
ethyl propionate and methyl acetate as well. No case of intramolecular ester interchange in a dicarboxylic molecule is recorded however.

The acid catalysed and base catalysed rearrangements proceed by different mechanisms. The mechanism for conversion of (XVI) to (XVIII) shouldexplain why the same acidic reagents do not rearrange (X) to (XXI). The base catalysed rearrangement mechanism should be equally applicable to conversion of (XXI) to (X).

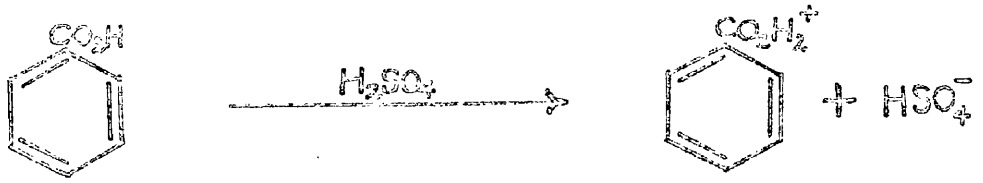
Acid Catalysed Rearrangement.

The isomerisation of 3-benzyloxy-2-ethoxycarbonyl-5--methoxyphenylacetic acid (XVI) to ethyl 3-benzyloxy-2-carboxy--5-methoxyphenylacetate (XVIII) is effected by phosphorus trichloride in dry chloroform in 75% yield, by thionyl chloride in 55% yield and by dry hydrogen chloride in dry chloroform in 20% yield. The figures quoted refer to yields of top purity material. Isomerisation does not take place in aqueous alcoholic acids.

Acylium ion formation is known to occur in ortho-disubstituted benzoic esters and benzoic acids[23,28,31]. For example, 2,4,6-trimethylbenzoic acid (mesitoic acid) in solvent sulphuric acid results in mesitoylium ion formation,



which explains the four-fold depression of freezing point of the solvent sulphuric acid[28,31]. Benzoic acid[28,31] gives a two-fold depression of freezing point, indicating that acylium ion formation does not take place. A freshly made solution



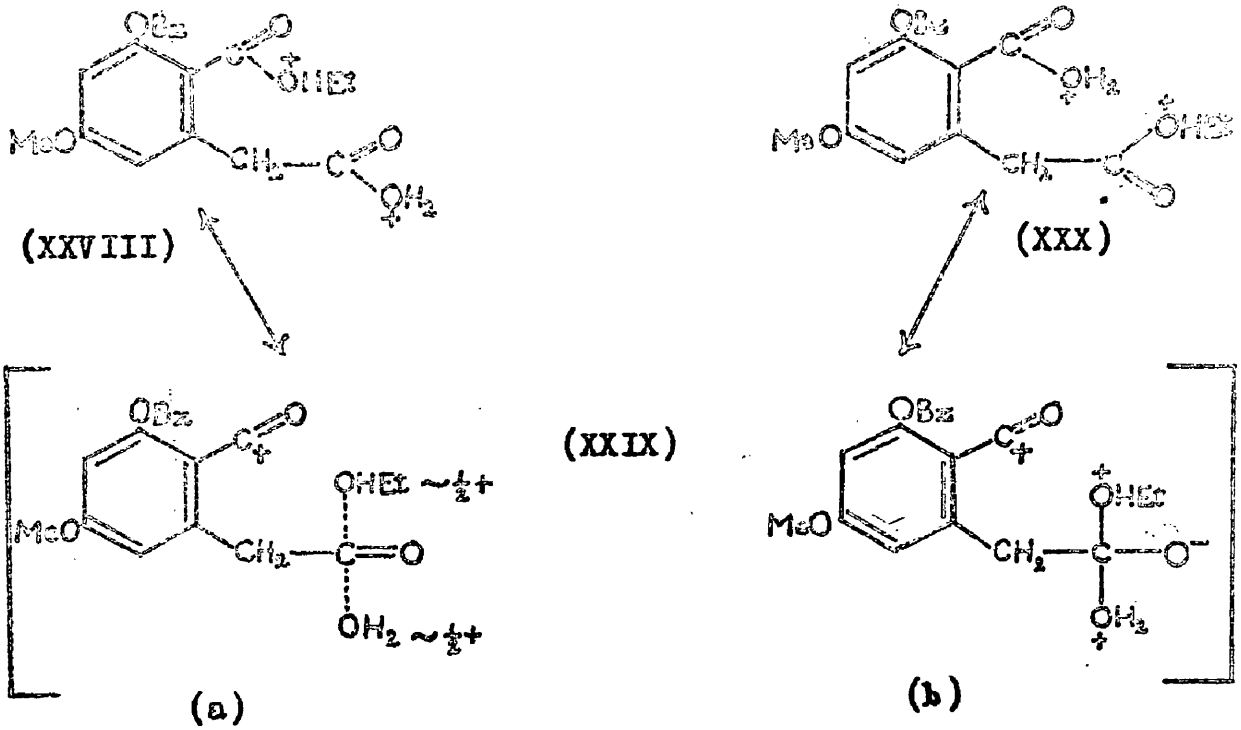
of methyl mesitoate in sulphuric acid on being poured into water gives a quantitative precipitate of mesitoic acid, while methyl benzoate on similar treatment remains unhydrolysed[28,30]. Similarly mesitoic acid is esterified by pouring a solution in sulphuric acid into alcohol, while benzoic acid is not thus esterified.[32,33] This behaviour is in contrast to the known retarding effects of ortho-substituents in the acid hydrolysis of benzoic esters in aqueous solvents, and in esterification of benzoic acids in alcoholic media[22,28,29,34-36]. The difference indicates that two mechanisms are involved. Thus in sulphuric acid reactions proceed by the unimolecular mechanism $A_{AC}1$, while in aqueous or alcoholic solvents the bimolecular mechanism $A_{AC}2$ is involved[28]. The strong retarding effects due to ortho -substituents on acid catalysed esterification and hydrolysis in aqueous and alcoholic solvents is well established,[22,29,34-36]

but it has also been noted that ortho-substitution in phenylacetic acids or esters does not retard esterification or hydrolysis.[29] Conversely there is little or no tendency to acyl ion formation in phenylacetic acids or esters. The retarding effect of ortho-substituents on a benzoic function in aqueous or alcoholic media depends on the size of the substituent rather than on its polarity.

In (XVI) the benzoic ester function is strongly hindered by the two large ortho-substituents. It is isomerised in anhydrous solvents by proton donating reagents. Rates of hydrolysis and esterification by the unimolecular mechanism should be increased by electropositive (electron donating) substituents in the acyl group,[27] since they assist heterolysis at the acyl carbon atom. The ortho-benzyl substituent is such an electropositive group, thus heterolysis of the benzoic oxonium ion would be assisted. Clearly the mechanism of conversion of (XVI) to (XVIII) involves formation of the acyl ion. Most of the information concerning acyl ion formation has been determined for 100% sulphuric acid solutions, but (XVI) and (X) could not be isomerised in this acid since they showed decomposition in it.

The first step, then, is protonation of both carboxylic functions to give (XXVIII). Due to steric crowding, and to an adjacent electropositive substituent, the acyl ion will be

formed by heterolytic fission. Since there is no steric driving force, and since there are no substituents to donate electrons to it, there is no tendency for the phenylacetic oxonium ion to dehydrate to the acyl ion. The liberated ethanol molecule from the benzoic function enters immediately into a normal bimolecular acid catalysed ($A_{AC}2$) esterification reaction with the phenylacetic oxonium ion to give (XXIX). It may be considered as taking place through a transition state (XXIXa), or an intermediate molecule (XXIXb).[27] The acylium ion function of (XXIX) accepts the eliminated water molecule to give



(XXX) which is the protonated form of ethyl 3-benzyloxy-2--carboxy-5-methoxyphenylacetate (XVIII). The driving force

in this isomerisation is primarily steric, the smaller bulk of the hydroxyl group being more acceptable to the strongly hindered benzoic function than the larger ethoxyl group, thus the reverse reaction is prevented. Such transfer of groups is facilitated by the proximity of the two carboxyl functions as shown by molecular models.

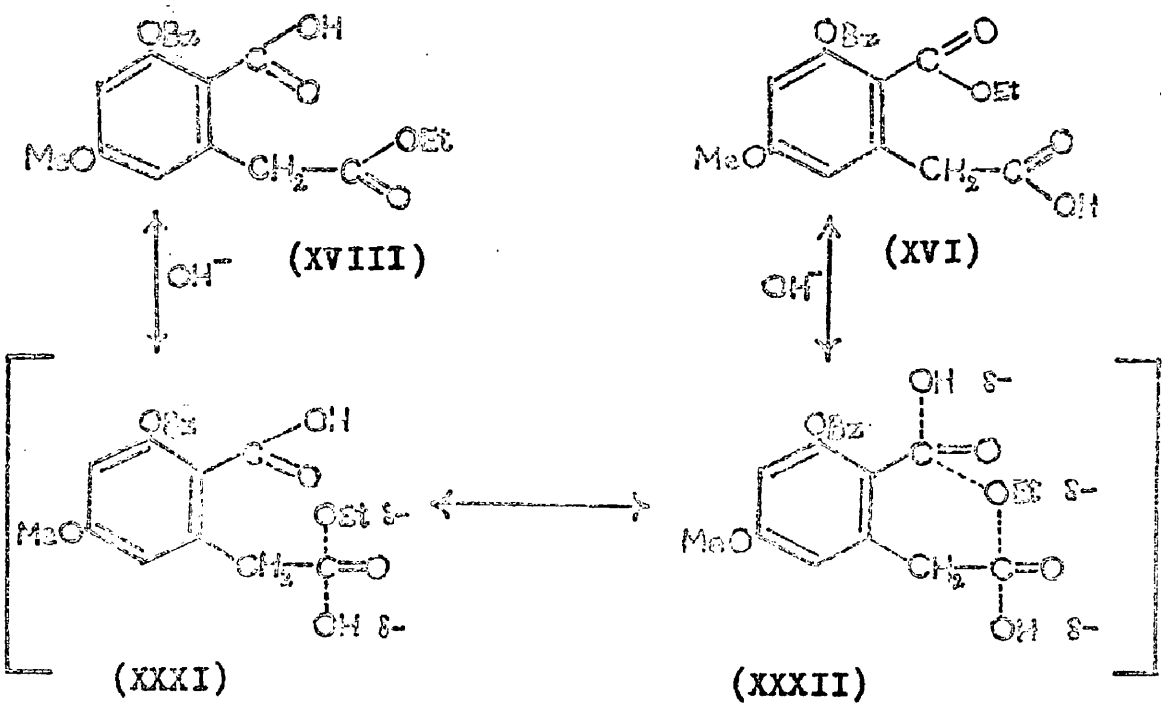
This mechanism may also furnish the explanation of why (X) is not rearranged to (XXI) by similar acidic conditions. In (X) the degree of steric hindrance of the benzoic ester group is much less than in (XVI), the possibility of benzoic acyl ion formation being thus much diminished,[28,30,52,53] also, due to the decreased steric hindrance in (X) there will be less tendency to exchange the smaller hydroxyl group for the larger ethoxyl group.

Alkali Catalysed Rearrangement.

The yields of 3-benzyloxy-2-ethoxycarbonyl-5-methoxy-phenylacetic acid (XVI) obtained by the action of alkali on ethyl 3-benxyloxy-2-carboxy-5-methoxyphenylacetate (XVIII) are high. The rearrangement has been accomplished by aqueous, aqueous ethanolic and aqueous methanolic alkali. Use of this latter reagent proves the reaction to be truly intramolecular, i.e. at not time during the reaction is the ethoxyl ion detached from the molecule.

It might seem that a possible mechanism involves the

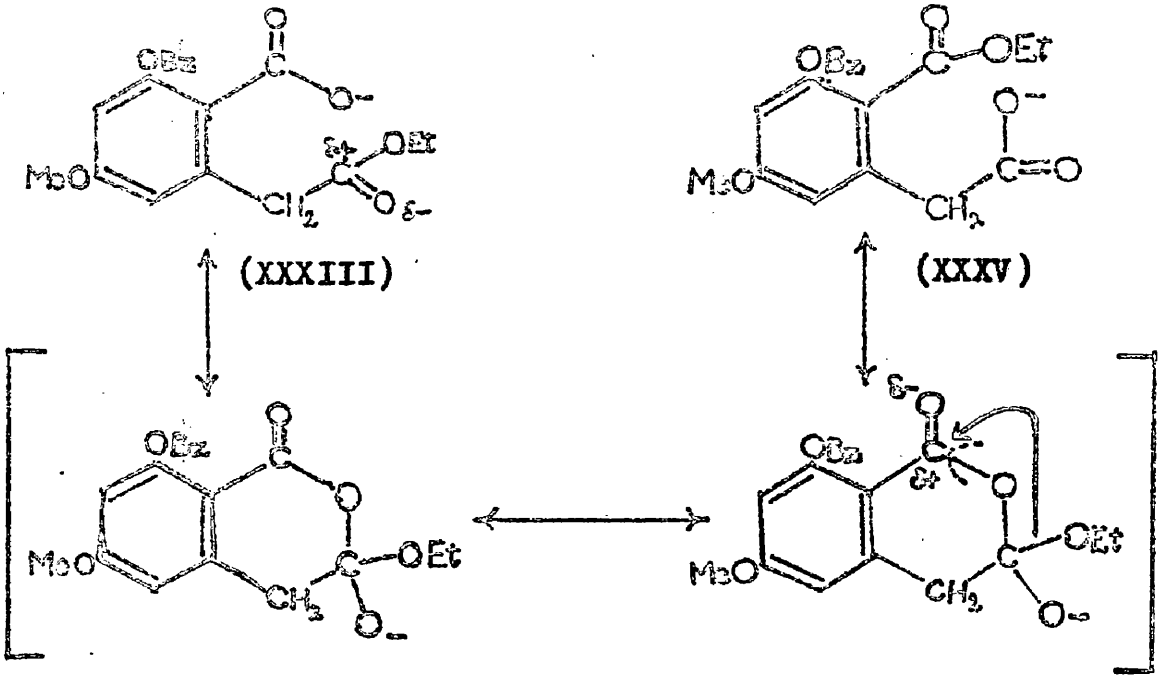
formation of an intermediate transition state (XXXII), a more complex form of (XXXI), the usual formulation for the intermediate in bimolecular basic hydrolysis with acyl-oxygen fission ($B_{AC}2$).[25]



For such a mechanism there is, however, no driving force, and, the steric effect of the substituents ortho to the benzoic carboxyl function would tend to prevent the approach of the larger ethoxyl group. A mechanism requiring a stronger driving force is thus required. In solution in alkali the carboxylate ion (XXXIII) will be present. Polarisation of the phenylacetic carbonyl will give the carbon atom of that carbonyl group a positive charge. Due to the proximity of the benzoic oxygen anion to the polarised phenylacetic carbonyl, as shown by

molecular models, there will be a tendency for the oxygen anion, by donating electrons, to form a bond with the charged carbon atom to give (XXXIV). The phenylacetic oxygen anion will exert a repulsive effect on the ethoxyl group. Polarisation of the benzoic carbonyl group will give that carbon atom a positive charge, which, due to the aforementioned proximity of the two carboxyl functions, will exert an attractive effect on the ethoxyl group. The combined repulsive and attractive effects on the ethoxyl group will cause transferance of that group as shown, with a simultaneous rupture of the benzoic acyl-oxygen bond to give (XXXV) the carboxyl ion of 3-benzyloxy-2-ethoxy-carbonyl-5-methoxyphenylacetic acid (XVI).

In the case of a possible reverse reaction, involving the



(XXXIII) (XXXV)

(XXXIV)

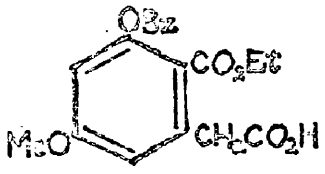
phenylacetic oxygen anion, the benzoic function in the intermediate complex would be negatively charged, therefore it is expected that adjacent electron donating substituents would retard the formation of such an intermediate.[26] The benzyl group is such an electron donating group, thus the reverse reaction is prevented from taking place, and the reaction is driven in one direction.

This mechanism is also applicable to the conversion of ethyl 2-carboxy-3-hydroxy-5-methoxyphenylacetate (XXI) to 2-ethoxycarbonyl-3-hydroxy-5-methoxyphenylacetic acid (X). The phenolic hydroxyl group in (XXI) bears a negative ionic charge in alkali, and is thus strongly electropositive (electron donating).[24] Thus, providing an even stronger retarding influence on the back reaction than in the case above. Furthermore, in the absence of the benzyl substituent, there will be less tendency for steric hindrance to prevent approach of the larger ethoxyl group.

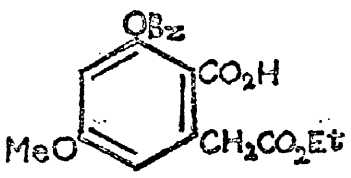
The Properties of the Acidic Benzyl Ether m.p.100-101°.

This aspect of the work is of more speculative interest, and is concerned with 3-benzyloxy-2-ethoxycarbonyl-5-methoxyphenylacetic acid (XVI). Preparation of (XVI) was carried out by refluxing methyl 2-ethoxycarbonyl-3-hydroxy-5-methoxyphenylacetate (XV) and benzyl chloride in solution in ethyl methyl ketone, for 72 hours, with potassium iodide to effect iodine

interchange, and anhydrous potassium carbonate. In an effort to speed up the reaction, ethyl methyl ketone was replaced by higher boiling diethyl ketone as solvent. This benzylation gave two products. The principle product was 3-benzyloxy-2-ethoxycarbonyl-5-methoxyphenylacetic acid (XVI), the other was an isomeric crystalline carboxylic acid m.p. 100-101°, 'compound 100', which gave no colouration with aqueous ferric chloride. The preparation described in the Experimental section shows a yield of 8% of 'compound 100' based on the weight of the starting material. The preparation was, however, not reproducible. Of eight further attempts to prepare the compound under the same conditions, six gave 3-benzyloxy-2-ethoxycarbonyl-5-methoxyphenylacetic acid (XVI) only, one gave a 30% yield of 'compound 100', and one gave a trace, and the balance as 3-benzyloxy-2-ethoxycarbonyl-5-methoxyphenylacetic acid (XVI). The total amount of 'compound 100' accumulated from the two successful preparations was 1.2 g. With this material a series of experiments was carried out to determine the structure of this compound.



(XVI)



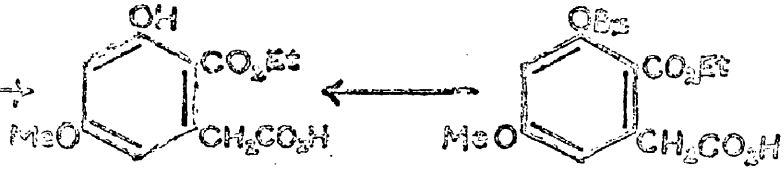
(XVIII)

The analytical data and titration Equivalent showed 'compound 100' to be isomeric with 3-benzyloxy-2-ethoxycarbonyl--5-methoxyphenylacetic acid (XVI) and ethyl 3-benzyloxy-2-carboxy--5-methoxyphenylacetate (XVIII). The m.p. of 'compound 100', was depressed on admixture with (XVI) and (XVIII), and its infrared spectrum was different from those of (XVI) and (XVIII).

'Compound 100' showed an infrared band in the carbonyl region at 1718 $cm.^{-1}$ in nujol mull and at 1721 $cm.^{-1}$ in chloroform. On the basis of the assignments which we have made for the carbonyl bands of the compounds prepared during this work, benzoic ester 1727-1712 $cm.^{-1}$ in nujol and 1724-1721 $cm.^{-1}$ in chloroform, and phenylacetic ester 1748-1733 $cm.^{-1}$ in nujol and 1742-1733 $cm.^{-1}$ in chloroform, the compound contains a benzoic ester function. 'Compound 100' is thus a benzoic ester, and its acid function must exist as a phenylacetic acid. 'Compound 100' was unchanged by the alkaline hydrolysis conditions which normally result in hydrolysis of a phenylacetic ester or in rearrangement of ethyl 3-benzyloxy-2-carboxy-5-methoxyphenylacetate (XVIII), further proof that it was a phenylacetic acid-benzoic ester. 'Compound 100' was similarly unaffected by refluxing with normal aqueous alcoholic hydrochloric acid. On treatment with diazomethane 'compound 100' gave an oily uncrystallisable methyl ester, which had a different infrared spectrum from the methyl esters of (XVI) and (XVIII). The methyl ester on mild alkaline

'Compound 100' ⟷ 'Compound 100' Methyl Ester

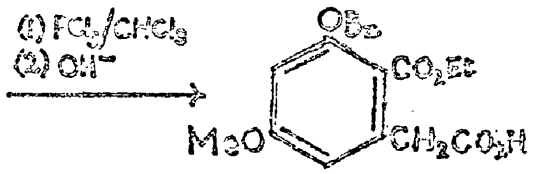
hydrolysis returned 'compound 100'. Debenzylation of 'compound 100' under the usual conditions gave 2-ethoxycarbonyl--3-hydroxy-5-methoxyphenylacetic acid (X). As was earlier mentioned, debenzylation of 3-benzyloxy-2-ethoxycarbonyl-5--methoxyphenylacetic acid (XVI) also gives (X).

'Compound 100' ⟶ 

(X) (XVI)

The conditions of the debenzylation were mild, and drastic rearrangement of the molecule was not possible. Thus it can be seen that the substituents on the aromatic ring occupy the same positions relative to each other that they do in (XVI).

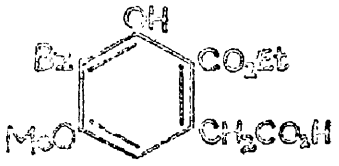
In the hope of bringing about ester-acid interchange analogous to that of 3-benzyloxy-2-ethoxycarbonyl-5-methoxyphenylacetic acid (XVI) and ethyl 3-benzyloxy-2-carboxy-5-methoxyphenylacetate (XVIII), 'compound 100' was treated with phosphorus trichloride in chloroform at room temperature under the usual conditions. The product was an uncrystallisable oil. Treatment of the oil with alkali gave a product m.p. 144-146° which was identical with (XVI).

'Compound 100' 

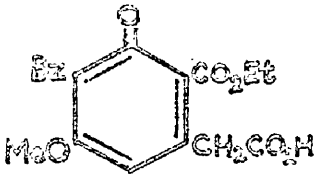
(XVI)

Structure of the Acidic Benzyl Ether m.p. 100-101°.

The most obvious possibility is that 'compound 100' is a C-benzyl acid of the type (XXXVI) or its tautomer (XXXVII). This type of structure is ruled out, however, since 'compound 100' gives no colouration with ferric chloride. Also, methylation of



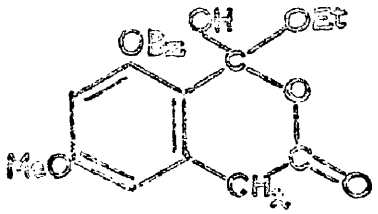
(XXXVI)



(XXXVII)

(XXXVI) with diazomethane would give the methyl ether diester, which on alkaline hydrolysis would not return the original acid (XXXVI) but its methyl ether. Finally, it is unlikely that (XXXVI) or (XXXVII) would be debenzylated by the conditions employed on 'compound 100'. The infrared carbonyl absorption of 'compound 100' (1721 $cm.^{-1}$) shows that the benzoic ester function is not intramolecularly, hydrogen bonded[9], hence there is no adjacent phenolic hydroxyl group. The carbonyl frequency also rules out (XXXVII) as a possibility, since (XXXVII) would show a band in the region of 1680 $cm.^{-1}$ due to the α,β ketone function.[31,42]

It might be suggested that 'compound 100' is a cyclic derivative of 3-benzyloxy-2-ethoxycarbonyl-5-methoxyphenylacetic acid (XVI) having structure (XXXVIII). A compound of structure



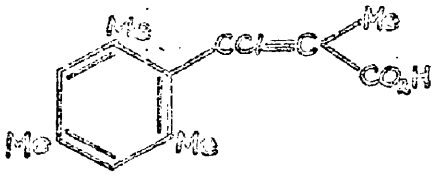
(XXXVIII)

(XXXVIII) would not, however, dissolve in cold aqueous sodium hydrogen carbonate with effervescence, and would ring-open under the hydrolytic conditions from which 'compound 100' was recovered unchanged.

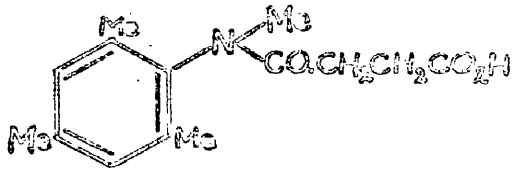
The possibility that 'compound 100' is a C-benzylated acid has been ruled out. Similarly the presence of a lactone ring has been disproved. The product of debenzylation, and the conversion of 'compound 100' to 3-benzyloxy-2-ethoxycarbonyl-5--methoxyphenylacetic acid (XVI) have proved that the four substituents on the aromatic ring occupy the positions relative to each other that they do in (XVI). We were thus driven to the idea that 'compound 100' and 3-benzyloxy-2-ethoxycarbonyl-5-methoxyphenylacetic acid (XVI) m.p. 144-146° are geometrical isomers of (XVI).

It is well known that rotation of the phenyl rings about

the 1,1' carbon-carbon bond in diphenyls is hindered by the steric repulsion of atoms or groups in the ortho-positions of the nuclei, thus giving rise to optical activity in these compounds (for leading references see Newman,[37] Ferguson[38] and Finar[39]). This repulsion is at a minimum when the rings are perpendicular to each other, for then the ortho-groups are at maximum distance from each other. Other types of compounds are known to exhibit

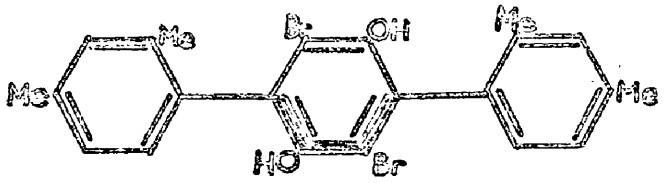


(XXXIX)

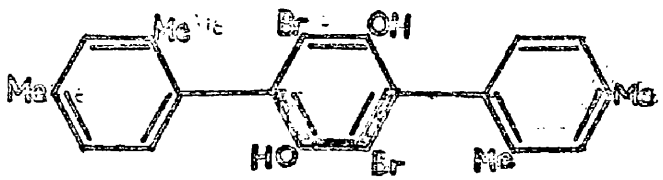


(XL)

optical isomerism due to steric hindrance,[38] for example (XXXIX) and (XL). It has also been observed[40,43,44] that terphenyl compounds can exhibit both geometrical and optical isomerism when suitable substituents are present to free rotation about the single bonds. For example the following cis- and trans-forms (XLI) and (XLII) have been prepared.[44] The two outside



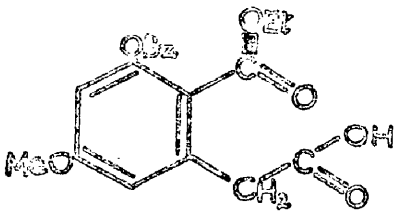
cis (XLI)



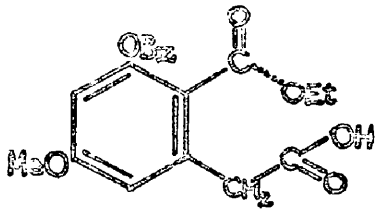
trans (XLII)

rings are held perpendicular to the centre ring. Since the cis- form does not possess a plane of symmetry, optical activity is possible. Thus the cis-form (XLI) has been resolved,[44] but the trans-isomer (XLII) is not resolvable since it possesses a plane of symmetry.

In the present case, the aromatic ring has three adjacent bulky substituents. Isomerism in which, due to restricted rotation about the ester-phenyl single bond, the benzoic ester group is held in (XLIII) with the ethoxyl group above the plane



(XLIII)



(XLIV)

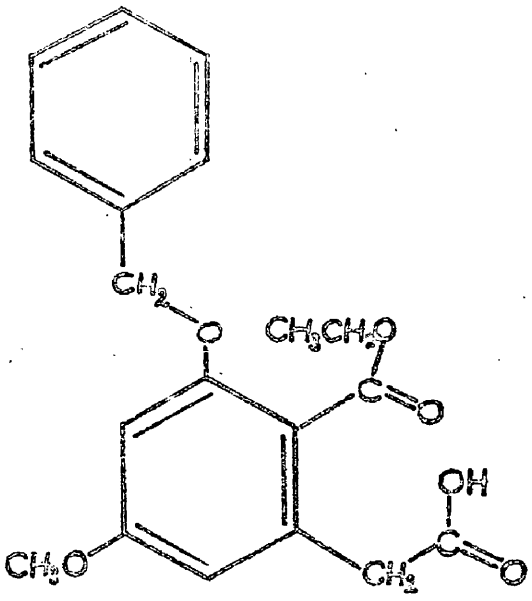
of the benzene ring and in (XLIV) with the ethoxyl group below the plane of the benzene ring, does not provide an explanation since (XLIII) and (XLIV) would be optical isomers only, not geometrical isomers having different physical and chemical properties.

The trans-form (XLV), in which steric crowding is at a minimum, is an obvious possibility. It possesses a plane of symmetry in the plane of the benzene rings and will be thus optically inactive. From models, the possibility of a cis-form (XLVI) having the two aromatic rings at an angle to each other, is also indicated. In the cis-form the groups are locked in the positions shown, and due to restricted rotation in

all three groups, cannot rotate freely about the single bonds to give the trans-form (XLV). The cis-isomer (XLVI) does not have a plane of symmetry; and a model of a non-superimposible mirror image has been made. Optical activity would thus be possible in the cis-form.

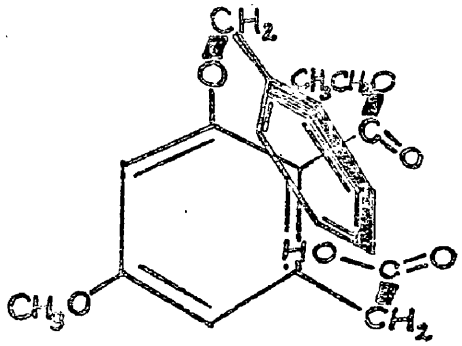
Many diphenyl compounds, the optical activity of which arise from restricted rotation, have been racemised by heat treatment.[37,39] Attempts were made to interconvert 3-benzyloxy-2-ethoxycarbonyl-5-methoxyphenylacetic acid (XVI) and 'compound 100' and their methyl and ethyl esters by heat treatment for prolonged periods, but no conversion was observed.

trans



(XLV)

cis



(XLVI)

Detection of optical activity in one of the compounds would have constituted reasonable proof of the existence of a cis- and a trans- isomer. An insufficient quantity of 'compound 100' was available, however, to attempt resolution. Attempted resolution of 3-benzyloxy-2-ethoxycarbonyl-5-methoxyphenylacetic acid (XVI) m.p. 144-146° by means of its quinine salt proved it to be optically inactive. Thus, if indeed the trans- and cis- forms of (XVI) do exist, the acid of m.p. 144-146° is the trans- isomer (XLV) while 'compound 100' is the cis- isomer (XLVI).

The system in (XVI) is complex, and although (XLVI) is the more obvious sterically hindered structure, models indicate that other highly hindered arrangements of the substituents might be possible. It has been shown that optical activity may arise in highly hindered polycyclic aromatic compounds from bending of the substituents out of the plane of the rings, as well as from deformation of the rings.[45-50] In the present case it is possible that bending of one or more of the substituents out of the plane of the ring, in one of the possible hindered arrangements of the substituents may contribute, to give rise to the second isomer of (XVI).

EXPERIMENTAL.

All melting points are uncorrected. Ultraviolet absorption spectra were determined in ethanol solution. Infrared comparison spectra were determined on Nujol mulls.

Ethyl 4-Carboxy-2-ethoxycarbonyl-3,5-dihydroxyphenylacetate. (Diethyl Hydrogen Orcinoltricarboxylate) (cf. Jerdan, J. Chem. Soc., 1899, 808). - A mixture of ethyl acetonedicarboxylate (40 g.), ethyl chloroacetate (10 g.) and magnesium powder (2 g.) was heated in a flask fitted with a short air condenser, at 180-190° (bath temperature) for 2 hours. Ethyl acetate was given off. The mixture was cooled to give a solid green mass, which was shaken for 30 minutes with concentrated hydrochloric acid (200 c.c.) and chloroform (100 c.c.). The solid dissolved. Water (200 c.c.) was added, and the chloroform layer separated off. The aqueous phase was extracted with chloroform (4 x 100 c.c.). The combined chloroform extract was washed with water, and with 2% aqueous sodium hydrogen carbonate (4 x 200 c.c.). The combined alkaline extract was acidified with dilute hydrochloric acid, when a yellow solid precipitated. The mixture was stirred occasionally, and after 30 minutes the solid was filtered off, washed with a small quantity of iced water, sucked dry and desiccated. The crude acid was decolourised by refluxing with charcoal in chloroform. Crystallisation from benzene-light

petroleum (b.p. 60-80°) gave ethyl 4-carboxy-2-ethoxycarbonyl--3,5-dihydroxyphenylacetate (10 g.) as plates m.p. 138-140° (lit., m.p. 141°).

Infrared spectrum: in nujol ν max. 1742, 1692, and 1645 cm.$^{-1}$,
in chloroform ν max. 1739, 1698 and 1647 cm.$^{-1}$.

Ethyl 2-Ethoxycarbonyl-3,5-dihydroxyphenylacetate. (cf. Nogami, J. Pharm. Soc. Japan, 1941, 61, 56-59 [C.A. 35, 4764^{e}]). - A mixture of ethyl 4-carboxy-2-ethoxycarbonyl-3,5-dihydroxyphenylacetate (8 g.), copper powder (2 g.) and quinoline (20 c.c.) was heated for 30 minutes at 190-195° (bath temperature). The mixture was cooled, ether (100 c.c.) added and the copper powder filtered off. The ethereal solution was washed with 2N hydrochloric acid (4 x 100 c.c.) and water, and dried (Na_2SO_4). Removal of the ether gave a dark brown solid which crystallised from acetone--light petroleum (b.p. 60-80°) to give ethyl 2-ethoxycarbonyl-3,5--dihydroxyphenylacetate (4.5 g.)as needles, m.p. 106-108°. (lit. m.p. 106-108°).

Infrared spectrum: in nujol ν max. 1712, and 1664 cm.$^{-1}$
in chloroform ν max. 1736 and 1661 cm.$^{-1}$

Ethyl 2-Ethoxycarbonyl-3-hydroxy-5-methoxyphenylacetate. - Ethyl 2-ethoxycarbonyl-3,5-dihydroxyphenylacetate (4 g.) in methanol (10 c.c.) was treated for 5 minutes with excess ethereal diazomethane. Removal of the solvents gave a gum which was

extracted with portions of boiling light petroleum (b.p.40-60°). Reduction of the combined light petroleum extract to small bulk gave ethyl 2-ethoxycarbonyl-3-hydroxy-5-methoxyphenylacetate as felted needles m.p. 62-64°.

Found: C,59.50; H,6.57%

$C_{14}H_{18}O_6$ requires: C,59.57; H,6.38%.

Light absorption: λ max. 2200 Å.(ε = 29,500), 2620 Å. (ε = 13,900) and 3020 Å.(ε = 6,600).

Infrared spectrum: in nujol ν max. 1733, and 1653 $cm.^{-1}$

in chloroform ν max. 1736, and 1661 $cm.^{-1}$

2-Ethoxycarbonyl-3-hydroxy-5-methoxyphenylacetic Acid.- Ethyl 2-ethoxycarbonyl-3-hydroxy-5-methoxyphenylacetate (200 mg.) was refluxed for 1 hour with aqueous sodium hydroxide (10 c.c.; 2N). The solution was cooled and acidified (Congo red) with hydrochloric acid (d,1.15). Crystals slowly separated from the solution. After 1 hour the crystals were filtered off, washed with water and sucked dry. Crystallisation from aqueous methanol gave 2-ethoxycarbonyl-3-hydroxy-5-methoxyphenylacetic acid (120 mg.) as needles, m.p. 186-188°.

Found: C,57.12; H,5.76%

$C_{12}H_{14}O_6$ requires: C,56.7; H,5.51%

Light absorption: λ max. 2160 Å. (ε = 29,500), 2600 Å.(ε = 13,450) and 3030 Å. (ε = 6,300).

Infrared spectrum: in nujol ν max. 1700 and 1667 $cm.^{-1}$

in chloroform ν max. 1718 and 1661 $cm.^{-1}$

The compound gave a red brown colour with ferric chloride solution.

3-Acetoxy-2-ethoxycarbonyl-5-methoxyphenylacetic Acid. - 2-Ethoxycarbonyl-3-hydroxy-5-methoxyphenylacetic acid (1 g.) was heated on a steam bath for 1 hour with pyridine (10 c.c.) and acetic anhydride (10 c.c.). Water (50 c.c.) was added and the solution warmed for a further 5 minutes, acidified with 2N hydrochloric acid to pH 1, and extracted with chloroform (3 x 50 c.c.). The combined chloroform-extract was washed with water and dried (Na_2SO_4). Evaporation of the chloroform gave a brown gum which crystallised from benzene-light petroleum (b.p. 60-80°) to give 3-acetoxy-2-ethoxycarbonyl-5-methoxyphenylacetic acid (900 mg.) as needles, m.p. 148-150°.

Found: C,56.70; H,5.21%

$C_{14}H_{16}O_7$ requires: C,56.76; H,5.41%

Light absorption: λ max. 2130 Å. (ε = 20,950) and 2520 Å. (ε = 10,370).

Infrared spectrum: in nujol ν max. 1757, and 1718 $cm.^{-1}$

in chloroform ν max. 1767, and 1721 $cm.^{-1}$

Methyl 2-Ethoxycarbonyl-3-hydroxy-5-methoxyphenylacetate. - A solution of 2-ethoxycarbonyl-3-hydroxy-5-methoxyphenylacetic acid (2 g.) in methanol (40 c.c.) was treated for 5 minutes with excess ethereal diazomethane. Removal of the solvents gave a gum which was extracted with portions of boiling light petroleum

(b.p. 40-60°). On evaporation of the combined light petroleum extract to small bulk, methyl 2-ethoxycarbonyl-3-hydroxy-5-methoxyphenylacetate crystallised as fine needles, m.p. 68-69°.

Found: C,57.92; H,6.25%

$C_{13}H_{16}O_6$ requires: C,58.2; H,6.02%

Light absorption: λ max. 2200 Å. (ε = 16,400), 2630 Å. (ε = 14,000) and 3020 Å. (ε = 6,900).

Infrared spectrum: in nujol ν max. 1739, and 1653 $cm.^{-1}$

in chloroform ν max. 1739 and 1658 $cm.^{-1}$

The compound in ethanol gave a red-brown colour with aqueous ferric chloride.

3-Benzyloxy-2-ethoxycarbonyl-5-methoxyphenylacetic Acid. - Methyl 2-ethoxycarbonyl-3-hydroxy-5-methoxyphenylacetate (2.8 g.), sodium iodidie (2 g.), anhydrous potassium carbonate (2 g.), benzyl chloride (2.5 c.c.) and methyl ethyl ketone (50 c.c.) were refluxed under anhydrous conditions for 72 hours. The solvent was evaporated off under reduced pressure, and water (150 c.c.) and ether (150 c.c.) added. The ethereal layer was separated off, washed with aqueous 5% sodium hydroxide (3 x 50 c.c.), water and dried (Na_2SO_4). Removal of the ether gave crude methyl 3-benzyloxy-2-ethoxycarbonyl-5-methoxyphenylacetate (3.5 g.) as a pale yellow gum. The gum was refluxed for 1 hour with potassium hydroxide (8 g.), water (8 c.c.) and ethanol (72 c.c.). Water (100 c.c.) was added and the ethanol distilled off under

reduced pressure. The almost complete solution was washed with chloroform (50 c.c.) and the aqueous phase acidified (Congo red) with dilute hydrochloric acid. The resulting emulsion was extracted with chloroform (3 x 50 c.c.) and the combined chloroform washings extracted with saturated aqueous sodium hydrogen carbonate (3 x 50 c.c.). The combined alkaline extract was acidified (Congo red) with dilute hydrochloric acid when a yellow precipitate was obtained. The solid was filtered off, sucked dry and desiccated. Crystallisation from acetone-light petroleum (b.p. 60-80°) gave 3-benzyloxy-2-ethoxycarbonyl-5-methoxyphenylacetic acid (1.9 g.) as needles, m.p. 144-146°.

Found: C, 66.50; H, 5.69%, equiv., 340.

$C_{19}H_{20}O_6$ requires: C, 66.27; H, 5.85%, equiv., 344.

Light absorption: λ max. 2080 Å. (ε = 46,700) and 2840 Å. (ε = 3,400).

Infrared spectrum: in Nujol ν max. 1724 and 1681 $cm.^{-1}$

in chloroform ν max. 1724 $cm.^{-1}$

Action of Alkali on 3-Benzyloxy-2-ethoxycarbonyl-5-methoxyphenylacetic Acid.,- 3-Benzyloxy-2-ethoxycarbonyl-5-methoxyphenylacetic acid (140 mg.) was refluxed for 24 hours with 30% aqueous potassium hydroxide (10 c.c.). The solution was cooled, ice was added and the solution acidified (Congo red) with dilute hydrochloric acid. After 1 hour the white solid was filtered off, washed with water, and sucked dry. Crystallisation from acetone-light petroleum (b.p. 60-80°) gave needles (110 mg.) of

m.p. and mixed m.p. with the starting material 143-145°. Comparison of the infrared spectra in Nujol also showed the material to be 3-benzyloxy-2-ethoxycarbonyl-5-methoxyphenylacetic acid.

Methyl 3-Benzyloxy-2-ethoxycarbonyl-5-methoxyphenylacetate. - 3-Benzyloxy-2-ethoxycarbonyl-5-methoxyphenylacetic acid (100 mg.) in methanol (5 c.c.) was treated for 1 hour with excess ethereal diazomethane. Removal of the solvents gave a gum which was extracted with portions of boiling light petroleum (b.p. 40-60°). Reduction of the combined light petroleum extract to small volume gave methyl 3-benzyloxy-2-ethoxycarbonyl-5-methoxyphenylacetate as felted needles, m.p. 39.5-41°.

Found: C,66.75; H,5.81%

$C_{20}H_{22}O_6$ requires: C,67.02; H,6.19%

Light absorption: λ max. 2100 Å. (ε = 34,800), 2500 Å. (ε = 6900) and 2860 Å. (ε = 3,500).

Infrared spectrum: in Nujol ν max 1748 and 1715 $cm.^{-1}$

in chloroform ν max. 1736 $cm.^{-1}$

Hydrolysis of Methyl 3-Benzyloxy-2-ethoxycarbonyl-5-methoxyphenylacetate to give 3-Benzyloxy-2-ethoxycarbonyl-5-methoxyphenylacetic Acid. - Methyl 3-benzyloxy-2-ethoxycarbonyl-5-methoxyphenylacetate (100 mg.) was refluxed for 1 hour with methanol (19 c.c.), potassium hydroxide (1 g.) and water (1 c.c.). Water (20 c.c.) was added and methanol distilled off under reduced pressure. The solution was cooled, acidified (Congo red) with

dilute hydrochloric acid and the white precipitate filtered off and sucked dry. Crystallisation of the solid from acetone-light petroleum (b.p. 60-80°) gave 3-benzyloxy-2-ethoxycarbonyl-5--methoxyphenylacetic acid as needles m.p. and mixed m.p. with an authentic specimen of the acid 144-146°. Comparison of the infrared spectra of the two samples proved them identical.

Hydrogenolysis of 3-Benzyloxy-2-ethoxycarbonyl-5-methoxyphenylacetic Acid. - A solution of 3-benzyloxy-2-ethoxycarbonyl--5-methoxyphenylacetic acid (190 mg.) in dry ethyl acetate (50 c.c.) was shaken for 6 hours with hydrogen at atmospheric pressure in the presence of palladised charcoal (200 mg., 2% $PdCl_2$ on charcoal) and magnesium oxide (100 mg.). The solids were filtered off, and the filtrate rejected. The solids were stirred with dilute hydrochloric acid (10 c.c.), and the mixture extracted with chloroform (3 x 50 c.c.). The combined chloroform extract was washed with water and saturated aqueous sodium hydrogen carbonate (3 x 20 c.c.). The combined alkaline extract was acidified (Congo red) with dilute hydrochloric acid. The crystals which separated on standing overnight were filtered off, washed with water and sucked dry. Recrystallisation from aqueous methanol gave 2-ethoxycarbonyl-3-hydroxy-5-methoxyphenylacetic acid (90 mg.) as needles m.p. 186-188°. The compound did not depress the m.p. when mixed with an authentic sample. The infrared spectra of the two samples were identical.

Ethyl 3-Benzyloxy-2-carboxy-5-methoxyphenylacetate. - (a) 3-Benzyloxy-2-ethoxycarbonyl-5-methoxyphenylacetic acid (1.2 g.) was suspended in a solution of phosphorus trichloride (850 mg.) and dry redistilled chloroform (230 c.c.) contained in a flask fitted with a calcium chloride tube. The mixture was shaken until the acid dissolved (30 minutes) and allowed to stand at room temperature for 24 hours. The chloroform was evaporated off under reduced pressure at room temperature. Benzene (100 c.c.) was added, and it also was evaporated under reduced pressure at room temperature to yield a pale yellow gum. The gum crystallised from benzene-light petroleum (b.p. 60-80°) to give ethyl 3-benzyloxy-2-carboxy-5-methoxyphenylacetate (920 mg.) as needles, m.p. 116-117.5°.

Found: C,66.43; H,6.05%; equiv., 341

$C_{19}H_{20}O_6$ requires: C,66.27; H,5.85%; equiv., 344.

Light absorption: λ max. 2100 Å. (ε = 33,900), 2580 Å. (ε = 6,000) and 2860 Å. (ε = 3,300).

Infrared spectrum: in Nujol ν max. 1736 and 1684 $cm.^{-1}$, and in chloroform ν max. 1736 $cm.^{-1}$.

(b) A solution of 3-benzyloxy-2-ethoxycarbonyl-5-methoxyphenylacetic acid (200 mg.) in thionyl chloride (2 c.c.) was refluxed for 10 minutes in a water bath at 85°. Excess thionyl chloride was removed by evaporation under reduced pressure at 40°. Benzene (10 c.c.) was added, and it also was evaporated off under reduced pressure at 40° to give an orange gum.

Crystallisation of the gum from benzene-light petroleum (b.p. 60-80°) gave ethyl 3-benzyloxy-2-carboxy-5-methoxyphenylacetate (110 mg) m.p. 116-117°. The compound did not depress the m.p. of the acid prepared in (a) above. The infrared spectra of the two samples were identical.

Found: C,66.42; H,6.03%

$C_{19}H_{20}O_6$ requires: C,66.27; H,5.85%.

(c) 3-Benzyloxy-2-ethoxycarbonyl-5-methoxyphenylacetic acid (500 mg.) was dissolved in a saturated solution of dry hydrogen chloride in dry redistilled chloroform (150 c.c.), and the solution warmed for 4 hours at 40°. The chloroform was evaporated under reduced pressure at room temperature. Benzene (50 c.c.) was added and it also was evaporated off at room temperature under reduced pressure to give a colourless gum. Fractional crystallisation of the gum from benzene-light petroleum (b.p. 60-80°) gave ethyl 3-benzyloxy-2-carboxy-5--methoxyphenylacetate (110 mg.) m.p. 116-117° and 3-benzyloxy-2--ethoxycarbonyl-5-methoxyphenylacetic acid (220 mg.), m.p. 144-146°. The identity of the products was confirmed by mixed m.p. with the authentic specimens, and by comparison of the infrared spectra.

3-Benzyloxy-2-ethoxycarbonyl-5-methoxyphenylacetic acid was recovered unchanged after similar treatment with hydrogen chloride in alcohols and aqueous alcohols.

The Action of Alkali on Ethyl 3-Benzyloxy-2-carboxy-5-methoxyphenylacetate. - (a) Ethyl 3-benzyloxy-2-carboxy-5-methoxyphenylacetate (200 mg.) was refluxed for 1 hour with 5% aqueous sodium hydroxide (20 c.c.). The solution was cooled, acidified (Congo red) with dilute hydrochloric acid, and the resulting solid filtered off and sucked dry. Crystallisation from acetone-light petroleum (b.p. 60-80°) gave 3-benzyloxy-2-ethoxycarbonyl-5-methoxyphenylacetic acid (140 mg.) as needles, m.p. 144-146°. The compound did not depress the m.p. when mixed with an authentic sample of the acid, m.p. 144-146°. The infrared spectra of both samples were identical.

(b) Ethyl 3-benzyloxy-2-carboxy-5-methoxyphenylacetate (250 mg.) was refluxed for 1 hour with potassium hydroxide (1 g.), water (1 c.c.) and methanol (19 c.c.). The solution was cooled, acidified (Congo red) with dilute hydrochloric acid and extracted with ether (3 x 20 c.c.). The ether extract was washed with water and dried (Na_2SO_4). Crystallisation from acetone-light petroleum (b.p. 60-80°) gave 3-benzyloxy-2-ethoxycarbonyl-5-methoxyphenylacetic acid (145 mg.) as needles, m.p. 143-145° and mixed m.p. with an authentic specimen, m.p. 143-145°. The infrared spectra of both specimens were identical.

The same product was obtained on hydrolysis of the compound with aqueous ethanolic potassium hydroxide.

(c) Ethyl 3-benzyloxy-2-carboxy-5-methoxyphenylacetate (20 mg.) was shaken with cold aqueous sodium hydroxide (20 c.c. $N/_{100}$). The acid slowly dissolved and the solution was allowed to stand at room temperature for 1 hour. The solution was acidified (Congo red) with dilute hydrochloric acid, and the precipitate filtered off and sucked dry. Crystallisation from benzene-light petroleum (b.p. 60-80°) returned ethyl 3-benzyloxy-2-carboxy-5--methoxyphenylacetate as needles m.p. 115-117° and mixed m.p. with an authentic specimen of this acid, 115-117°. Comparison of their infrared spectra proved them identical.

Ethyl 3-Benzyloxy-2-methoxycarbonyl-5-methoxyphenylacetate.- Ethyl 3-benzyloxy-2-carboxy-5-methoxyphenylacetate (100 mg.) in methanol (5 c.c.) was treated for 1 hour with excess ethereal diazomethane. Evaporation of the solvents gave a gum which was extracted with portions of boiling light petroleum (b.p. 40-60°). The combined extract was concentrated and the crystalline solid which slowly separated was further recrystallised from light petroleum (b.p. 40-60°) to give ethyl 3-benzyloxy-2-methoxycarbonyl-5-methoxyphenylacetate as felted needles, m.p. 74-75°

Found: C,66.84; H,6.28%

$C_{20}H_{22}O_6$ requires: C,67.02; H,6.19%.

Light absorption: λ max. 2100 Å. (ε = 35,500), 2500 Å. (ε = 6,500) and 2860 Å. (ε = 3400).

Infrared spectrum: in Nujol ν max. 1736 and 1712 cm.$^{-1}$

in chloroform ν max. 1733 cm.$^{-1}$

Ethyl 3-Benzyloxy-2-ethoxycarbonyl-5-methoxyphenylacetate.- (a) Ethyl 3-benzyloxy-2-carboxy-5-methoxyphenylacetate (100 mg.) in methanol (4 c.c.) was treated for 1 hour with excess ethereal diazoethane. Evaporation of the solvents gave a colourless gum which did not solidify.

Infrared spectrum: ν max. in Nujol 1733 $cm.^{-1}$

(b) 3-Benzyloxy-2-ethoxycarbonyl-5-methoxyphenylacetic acid (100 mg.) in methanol (4 c.c.) was treated for 1 hour with diazoethane as described in (a) above. The product was a colourless gum which did not solidify. The infrared spectrum of the gum was identical with that of the ester prepared in (a) above.

Hydrolysis of Ethyl 3-Benzyloxy-2-ethoxycarbonyl-5--methoxyphenylacetate to 3-Benzyloxy-2-ethoxycarbonyl-5-methoxyphenylacetic Acid. - Ethyl 3-benzyloxy-2-ethoxycarbonyl-5--methoxyphenylacetate (50 mg.), from preparation (a) above, was refluxed for 1 hour with methanol (9.5 c.c.), potassium hydroxide (0.5 g.) and water (0.5 c.c.) and worked up in the usual way. Crystallisation of the solid product from acetone--light petroleum (b.p. 60-80°) gave 3-benzyloxy-2-ethoxycarbonyl--5-methoxyphenylacetic acid as needles m.p. and mixed m.p. with an authentic specimen of the acid, 144-146°. The infrared spectra of the two samples were identical.

The same product was obtained by similar hydrolysis of the ester prepared in (b) above.

Ethyl 2-Carboxy-3-hydroxy-5-methoxyphenylacetate. - Ethyl 3-benzyloxy-2-carboxy-5-methoxyphenylacetate (250 mg.) in dry redistilled ethyl acetate (70 c.c.) was shaken for 6 hours with hydrogen at atmospheric pressure in the presence of palladised charcoal (250 mg., 2½% $PdCl_2$ on charcoal) and magnesium oxide (100 mg.). The solids were filtered off, and the filtrate rejected. The solids were stirred with dilute hydrochloric acid (10 c.c.) and the mixture extracted with chloroform (3 x 50 c.c.). The combined chloroform extract was washed with water and with saturated aqueous sodium hydrogen carbonate (3 x 20 c.c.). The combined alkaline extract was acidified (Congo red) with dilute hydrochloric acid. The crystalline precipitate was filtered off, washed with water and sucked dry. Recrystallisation from benzene-light petroleum (b.p. 60-80°) gave ethyl 2-carboxy-3-hydroxy-5-methoxyphenylacetate (140 mg.) as needles, m.p.119-120°.

Found: C,57.10; H,5.79%

$C_{12}H_{14}O_6$ requires: C,56.69; H,5.55%

Light absorption: λmax 2140 Å. (ε = 25,400), 2600 Å (ε = 11,300) and 3020 Å. (ε = 5,700).

Infrared spectrum: in Nujol ν max. 1736 $cm.^{-1}$,

in chloroform ν max. 1736 and 1656 $cm.^{-1}$

The compound in ethanol gives a red-brown colour with aqueous ferric chloride.

2-Ethoxycarbonyl-3-hydroxy-5-methoxyphenylacetic Acid from Ethyl 2-Carboxy-3-hydroxy-5-methoxyphenylacetate. - Ethyl 2-carboxy-3-hydroxy-5-methoxyphenylacetate (50 mg.) in methanol (5 c.c.) was treated for 5 minutes with excess ethereal diazoethane. Removal of the solvents gave a gum which crystallised from light petroleum (b.p. 40-60°) to give ethyl 2-ethoxycarbonyl-3-hydroxy-5-methoxyphenylacetate as felted needles m.p. and mixed m.p. 61-64° with an authentic sample of the compound. The infrared spectra of the two samples were identical.

The ethyl 2-ethoxycarbonyl-3-hydroxy-5-methoxyphenylacetate (25 mg.) thus obtained was refluxed for 1 hour with 5% aqueous methanolic potassium hydroxide (5 c.c.) and the product worked up in the usual manner. Crystallisation of the solid from aqueous methanol gave 2-ethoxycarbonyl-3-hydroxy-5-methoxyphenylacetic acid as needles, m.p. and mixed m.p. 185-187° with an authentic sample of the acid. The infrared spectra of the two samples were identical.

Action of Alkali on Ethyl 2-Carboxy-3-hydroxy-5-methoxyphenylacetate to give 2-Ethoxycarbonyl-3-hydroxy-5-methoxyphenylacetic Acid. - Ethyl 2-carboxy-3-hydroxy-5-methoxyphenylacetate (50 mg.) was refluxed with 10% aqueous potassium hydroxide (5 c.c.) for 2 hours. The cooled solution was acidified

(Congo red) with dilute hydrochloric acid. The crystalline precipitate which slowly separated was filtered off, sucked dry and crystallised from aqueous methanol to give 2-ethoxycarbonyl-3-hydroxy-5-methoxyphenylacetic acid as needles, m.p. and mixed m.p. with an authentic specimen of the acid 185-187°. The two samples had identical infrared spectra.

Action of Phosphorus Trichloride on 2-Ethoxycarbonyl-3-hydroxy-5-methoxyphenylacetic Acid. - 2-Ethoxycarbonyl-3-hydroxy-5-methoxyphonylacetic acid (100 mg.) was suspended in a solution containing phosphorus trichloride (240 mg.) and dry redistilled chloroform (50 c.c.). The mixture was shaken until the acid dissolved, and the solution allowed to stand at room temperature for 24 hours. The chloroform was evaporated off under reduced pressure at room temperature. Benzene (10 c.c.) was added, and it also was evaporated off under reduced pressure at room temperature to yield a white solid. The solid was crystallised from acetone-light petroleum b.p. 60-80° as needles, m.p. and mixed m.p. with an authentic sample of 2-ethoxycarbonyl-3-hydroxy-5-methoxyphenylacetic acid 182-184°. The infrared spectra of the two samples were identical.

2-Ethoxycarbonyl-3-hydroxy-5-methoxyphenylacetic acid on treatment with dry hydrogen chloride in dry redistilled chloroform, as described for 3-benzyloxy-2-ethoxycarbonyl-5-methoxyphenylacetic acid, returned the starting material unchanged.

Synthesis of Ethyl 3-Benzyloxy-2-methoxycarbonyl-5-methoxy-phenylacetate.

Methyl 4-Carboxy-3,5-dihydroxy-2-methoxycarbonylphenyl-acetate. - A mixture of methyl acetone dicarboxylate (50 g.), ethyl chloracetate (12.5 g.) and magnesium powder (2.5 g.) was heated in a flask fitted with a short air condenser at 180-190° (bath temperature) for 2 hours. Magnesium powder (500 mg.) was added and heating continued for a further 5 minutes. The cooled mixture was shaken with chloroform (100 c.c.) and concentrated hydrochloric acid (100 c.c.) until the solid had dissolved. The chloroform layer was separated, washed with water and extracted with saturated aqueous sodium hydrogen carbonate (3 x 100 c.c.). The combined alkaline extract was acidified (Congo red) with dilute hydrochloric acid and allowed to stand overnight. The yellow precipitate was filtered off, washed with a little iced water, sucked dry and desiccated. Crystallisation of the solid from benzene (charcoal) gave methyl 4-carboxy-3,5-dihydroxy-2-methoxycarbonylphenylacetate (12.75 g.) as plates, m.p. 152-154°.

Found: C,51.02; H,4.53%

$C_{12}H_{12}O_8$ requires : C,50.71; H,4.26%

Light absorption: λ max. 2240 Å. (ε = 21,800), 2380 Å. (ε = 17,100) and 3200 Å. (ε = 5,500).

Infrared spectrum: in Nujol ν max. 1742 and 1692 cm.$^{-1}$

in chloroform ν max. 1742, 1697, and 1656 cm.$^{-1}$.

The compound in ethanol gave a red-brown colouration with aqueous ferric chloride.

Methyl 3,5-Dihydroxy-2-methoxycarbonylphenylacetate. - A mixture of methyl 4-carboxy-3,5-dihydroxy-2-methoxycarbonylphenylacetate (4 g.), quinoline (2 c.c.), copper powder (1 g.) and carborundum chips was heated for 40 minutes at 175-185° (bath temperature). To the cooled mixture was added chloroform (100 c.c.) and the solids filtered off. The chloroform extract was washed with dilute hydrochloric acid (3 x 100 c.c.), saturated aqueous sodium hydrogen carbonate (3 x 50 c.c.), water and dried (Na_2SO_4). Removal of the solvent gave a brown gum which crystallised from benzene-light petroleum (b.p. 60-80°) to give methyl 3,5-dihydroxy-2-methoxycarbonylphenylacetate (900 mg.) as needles, m.p. 148-150°.

Found: C,54.95; H,5.30%

$C_{11}H_{12}O_6$ requires: C,54.99; H,5.04%.

Light absorption: λ max. 2160 Å. (ε = 20,300), 2650 Å. (ε = 10,900) and 3040 Å. (ε = 6,100).

Infrared spectrum: in Nujol ν max. 1706 and 1653 cm.$^{-1}$

in chloroform ν max. 1736 and 1667 cm.$^{-1}$.

The compound in ethanol gave a red-brown colour with aqueous ferric chloride.

Methyl 3-Hydroxy-5-methoxy-2-methoxycarbonylphenylacetate. - A solution of methyl 3,5-dihydroxy-2-methoxycarbonylphenylacetate (100 mg.) in methanol (2 c.c.) was treated for 5 minutes with excess ethereal diazomethane. Removal of the solvents gave a gum which was extracted with portions of boiling light petroleum (b.p. 40-60°). On concentration of the combined petroleum extract crystals separated slowly. Recrystallisation from light petroleum (b.p. 40-60°) gave methyl 3-hydroxy-5-methoxy--2-methoxycarbonylphenylacetate as felted needles, m.p. 75-77°.

Found: C,57.05; H,5.69%

$C_{12}H_{14}O_5$ requires: C,56.69; H,5.55%

Light absorption: λ max 2200 Å. (ϵ = 14,600), 2630 Å. (ϵ = 12,700) and 3010 Å. (ϵ = 6,000).

Infrared spectrum: in Nujol ν max. 1739 and 1661 $cm.^{-1}$

in chloroform ν max. 1739 and 1667 $cm.^{-1}$

The compound in ethanol gave a red-brown colour with aqueous ferric chloride.

3-Benzyloxy-5-methoxy-2-methoxycarbonylphenylacetic Acid. - Methyl 3-hydroxy-5-methoxy-2-methoxycarbonylphenylacetate (400 mg.), anhydrous potassium carbonate (400 mg.), sodium iodide (400 mg.), ethyl methyl ketone (10 c.c.) and benzyl chloride (0.55 c.c.) were refluxed together for 72 hours. The solvent was evaporated off under reduced pressure and ether (20 c.c.) and water (20 c.c.) added. The ether layer was separated off, washed with water, 5% aqueous sodium hydroxide (3 x 20 c.c.) and water, and dried

(Na_2SO_4). Removal of the ether gave methyl 3-benzyloxy-5--methoxy-2-methoxycarbonylphenylacetate as a clear oil (500 mg.). The oil was refluxed for 2 hours with methanol (18 c.c.), potassium hydroxide (2 g.) and water (2 c.c.). Water (20 c.c.) was added and methanol distilled off under reduced pressure. The cooled solution was acidified (Congo red) with dilute hydrochloric acid, and the resulting emulsion extracted with ether (3 x 20 c.c.). The combined ether extract was washed with aqueous sodium hydrogen carbonate (3 x 20 c.c.) and the alkaline extract acidified (Congo red) with dilute hydrochloric acid. The solid was filtered off, washed with water and sucked dry. Crystallisation from acetone-light petroleum (b.p. 60-80°) gave 3-benzyloxy-5-methoxy-2-methoxycarbonylphenylacetic acid (280 mg.) as needles, m.p. 147-149°.

Found: C,65.24; H,5.31%

$C_{18}H_{18}O_6$ requires: C,65.45; H,5.48%.

Light absorption: λmax. 2120 Å. (ε = 35,700), 2480 Å. (ε = 6,400) and 2850 Å. (ε = 3,400).

Infrared spectrum: in Nujol ν max. 1727 $cm.^{-1}$

in chloroform ν max. 1724 $cm.^{-1}$

Ethyl 3-Benzyloxy-5-methoxy-2-methoxycarbonylphenylacetate from 3-Benzyloxy-5-methoxy-2-methoxycarbonylphenylacetic Acid. - 3-Benzyloxy-5-methoxy-2-methoxycarbonylphenylacetic acid (100 mg.) in methanol (2 c.c.) was treated for 1 hour with excess ethereal diazoethane. Removal of the solvent gave a gum which was

extracted with portions of light petroleum (b.p. 60-80°). On concentration of the combined extract, crystals slowly separated. Repeated recrystallisation from light petroleum (b.p. 40-60°) gave ethyl 3-benzyloxy-5-methoxy-2-methoxycarbonylphenylacetate as felted needles, m.p. 71-73°. This compound had m.p. 71-74° on admixture with ethyl 3-benzyloxy-5-methoxy-2-methoxycarbonylphenylacetate, m.p. 74-75° prepared by methylation of ethyl 3-benzyloxy-2-carboxy-5-methoxyphenylacetate. The infrared spectra of the two samples were identical.

Hydrolysis of Ethyl 3-Benzyloxy-2-methoxycarbonyl-5-methoxyphenylacetate to 3-Benzyloxy-5-methoxy-2-methoxycarbonylphenylacetic Acid. - Ethyl 3-benzyloxy-2-methoxycarbonyl-5-methoxyphenylacetate (50 mg.) obtained by methylation of ethyl 3-benzyloxy-2-carboxy-5-methoxyphenylacetate, was refluxed for 1 hour with methanol (19 c.c.), potassium hydroxide (1 g.) and water (c.c.). Water (20 c.c.) was added and methanol distilled off. The cooled solution was acidified (Congo red) with dilute hydrochloric acid, the white precipitate filtered off, washed with water and sucked dry. Crystallisation of the white solid from acetone-light petroleum gave 3-benzyloxy-5-methoxy-2-methoxycarbonylphenylacetic acid as clusters of needles, m.p. 149-150°. The substance had m.p. 147-150° on admixture with an authentic specimen, m.p. 147-149°. The infrared spectra of both samples were identical.

The Anhydride of Ethyl 3-Benzyloxy-2-carboxy-5-methoxyphenylacetate. - A solution of 3-benzyloxy-2-ethoxycarbonyl--5-methoxyphenylacetic acid (400 mg.) in phosphorus trichloride (300 mg.) and dry redistilled chloroform (12 c.c.) was refluxed for 20 minutes in a water bath at 70°. The chloroform solution was decanted from the scum of phosphorous acid. The chloroform was removed under reduced pressure at room temperature, benzene (50 c.c.) was added and it also was removed under reduced pressure at room temperature to give a yellow gum. Crystallisation of the gum from benzene-light petroleum (b.p. 50-80°) gave the anhydride of ethyl 3-benzyloxy-2-carboxy-5-methoxyphenylacetate (220 mg.) as yellow plates m.p. 170-173°. After two days the m.p. of the same sample had dropped to 155-162°.

Found: mean C,67.29; H,5.28%; M.W. (Rast) 610

$C_{38}H_{38}O_{11}$ requires: C,68.08; H,5.67%; M.W. 671.

Light absorption: λ max. 2100 Å. (ε = 60,200), 2670 Å. (ε = 27,400) and inflexion at 3040 Å. (ε = 5,000).

Infrared spectrum: in Nujol ν max. 1789, 1751, 1099, and inflexion at 1730 $cm.^{-1}$,

in chloroform ν max. 1796, 1750, 1097 and inflexion at 1730 $cm.^{-1}$.

The compound did not dissolve in cold aqueous sodium hydrogen carbonate, nor in cold 5% aqueous sodium hydroxide.

The anhydride was also prepared by similar treatment of ethyl 3-benzyloxy-2-carboxy-5-methoxyphenylacetate with phosphorus

trichloride in dry chloroform.

Hydrolysis of the Anhydride of Ethyl 3-benzyloxy-2--carboxy-5-methoxyphenylacetate to 3-Benzyloxy-2-ethoxycarbonyl--5-methoxyphenylacetic Acid. - The anhydride of ethyl 3-benzyloxy-2-carboxy-5-methoxyphenylacetate (100 mg.) was refluxed for 1 hour with potassium hydroxide (500 mg.), methanol (9 c.c.) and water (1 c.c.). The yellow colour rapidly disappeared. Water (20 c.c.) was added and methanol was distilled off under reduced pressure. Acidification of the cooled solution with dilute hydrochloric acid gave a precipitate, which was filtered off, sucked dry and crystallised from acetone-light petroleum (b.p. 60-80°) to give 3-benzyloxy--2-ethoxycarbonyl-5-methoxyphenylacetic acid (72 mg.) as needles, m.p. 144-146°. The compound did not depress the m.p. when mixed with an authentic specimen of the acid. The infrared spectra of both samples were identical.

Preparation of the Compound m.p. 100°. - Methyl 2-ethoxycarbonyl-3-hydroxy-5-methoxyphenylacetate (2.7 g.), sodium iodide (2 g.), anhydrous potassium carbonate (2 g.), benzyl chloride (2.5 c.c.) and diethyl ketone (25 c.c.) were refluxed under anhydrous conditions for 72 hours. The solvent was evaporated off under reduced pressure and water (150 c.c.) and ether (150 c.c.) added. The ether layer was separated off, washed with aqueous

5% sodium hydroxide (3 x 50 c.c.), water and dried (Na_2SO_4). Removal of the ether gave a gum which was refluxed for 1 hour with potassium hydroxide (8 g.), water (8 c.c.) and ethanol (72 c.c.). Water was added, ethanol distilled off under reduced pressure, and the almost complete solution washed with chloroform (50 c.c.). The aqueous phase was acidified (Congo red) with dilute hydrochloric acid, the resulting emulsion extracted with chloroform (3 x 50 c.c.) and the combined chloroform washings extracted with saturated aqueous sodium hydrogen carbonate (3 x 50 c.c.). The combined alkaline extract was acidified (Congo red) with hydrochloric acid and the resulting yellow precipitate filtered off, washed with water, sucked dry and desiccated. Fractional crystallisation from acetone--light petroleum (b.p. 60-80°) gave crop I (220 mg.) as needles m.p. 100-101°, and crop II (900 mg.) as needles m.p. 142-144°.

The material from crop II, on admixture with 3-benzyloxy--2-ethoxycarbonyl-5-methoxyphenylacetic acid m.p. 144-146°, had m.p. 142-145°. The infrared spectra of the two samples were identical. Crop II is therefore 3-benzyloxy-2-ethoxycarbonyl-5-methoxyphenylacetic acid.

The material from Crop I on admixture with 3-benzyloxy--2-ethoxycarbonyl-5-methoxyphenylacetic acid had m.p. 89-95°.

Found: C,66.61; H,6.01%; equiv., 339,

$C_{20}H_{22}O_6$ requires: C,67.02; H,6.19%; equiv., 344.

Light absorption: λ max. 2120 Å. (ε = 31,800), 2480 Å. (ε = 6,200) and 2860 Å. (ε = 3,200)

Infrared spectrum: in Nujol ν max. 1727 $cm.^{-1}$,

in chloroform ν max. 1727 $cm.^{-1}$

The compound in ethanol gave no colour with aqueous ferric chloride. The compound dissolved with effervescence in cold aqueous sodium hydrogen carbonate.

The methyl ester was made by treatment of the compound in methanol for 1 hour with excess ethereal diazomethane. Removal of the solvents gave an oil, which did not crystallise.

Infrared spectrum: in Nujol ν max. 1727 $cm.^{-1}$.

Action of Alkali on Compound m.p. 100-101°. - The compound m.p. 100-101° (50 mg.) was refluxed for 2 hours with 10% aqueous potassium hydroxide. The cooled solution was acidified and the crystals which slowly separated were filtered off, washed with water and sucked dry. Recrystallisation from acetone-light petroleum (b.p. 60-80°) returned the starting material as needles m.p. and mixed m.p. 99-101°. The infrared spectra of the two samples were identical.

Action of Acid on Compound m.p. 100-101°. - The compound m.p. 100-101° (50 mg.) was refluxed for 1 hour with concentrated

hydrochloric acid (0.5 c.c.) and methanol (7 c.c.). Water (10 c.c.) was added and the emulsion extracted with chloroform (3 x 5 c.c.). The combined chloroform extract was washed with water, and saturated aqueous sodium hydrogen carbonate (3 x 5 c.c.). The combined alkaline extract was acidified (Congo red) with dilute hydrochloric. The resulting white precipitate was filtered off, washed with water and sucked dry. Recrystallisation from acetone-light petroleum (b.p. 60-80°) returned the starting material as needles m.p. and mixed m.p. 98-100°. The infrared spectra of the two samples were identical.

Hydrolysis of the Methyl Ester of the Compound m.p. 100-101° to give the Compound m.p. 100-101°. - The oily methyl ester of the compound m.p. 100-101° (50 mg.) was refluxed for 1 hour with 5% aqueous ethanolic potassium hydroxide (10 c.c.). Water (10 c.c.) was added and ethanol distilled of under reduced pressure. The solution was acidified (Congo red) with dilute hydrochloric acid, the solid precipitate filtered off, washed with water and sucked dry. Crystallisation from acetone-light potroleum (b.p. 60-80°) gave the compound m.p. 100-101° as needles of m.p. and mixed m.p. 98-100°. The infrared spectra of the two specimens were identical.

Hydrogenolysis of the Compound m.p. 100-101° to 2-Ethoxycarbonyl-3-hydroxy-5-methoxyphenylacetic Acid. - A solution of

the compound of m.p. 100-101° (150 mg.) in dry ethyl acetate (50 c.c.) was shaken for 6 hours with hydrogen at atmospheric pressure in the presence of palladised charcoal (250 mg., 2½% $PdCl_2$ on charcoal) and magnesium oxide (100 mg.). The solids were filtered off and the filtrate rejected. The solids were stirred with dilute hydrochloric acid (10 c.c.) and the mixture extracted with chloroform (3 x 50 c.c.). The combined chloroform extract was washed with water and with saturated aqueous sodium hydrogen carbonate (3 x 20 c.c.). The combined alkaline extract was acidified (Congo red) with dilute hydrochloric acid. The crystalline precipitate which slowly separated was filtered off, washed with water and sucked dry. Recrystallisation from aqueous methanol gave 2-ethoxycarbonyl-3-hydroxy-5-methoxy-phenylacetic acid as needles (70 mg.) m.p. 186-188°, and mixed m.p. 186-188° with an authentic specimen. The infrared spectra of both samples were identical.

Conversion of the Compound m.p. 100-101° to 3-Benzyloxy--2-ethoxycarbonyl-5-methoxyphenylacetic Acid. - To a solution of the compound m.p. 100-101° (200 mg.) in dry chloroform (40 c.c.) was added phosphorus trichloride (140 mg.). The solution was left at room temperature for 24 hours. The chloroform was evaporated off under reduced pressure at room temperature. Benzene (20 c.c.) was added, and it was similarly removed at

room temperature to give a pale yellow uncrystallisable oil.

The oil (210 mg.) was refluxed for 1 hour with methanol (19 c.c.), potassium hydroxide (1 g.) and water (1 c.c.). Water (20 c.c.) was added and methanol distilled off under reduced pressure. The solution was acidified (Congo red) with dilute hydrochloric acid and the resulting white precipitate filtered off, washed with water and sucked dry. Crystallisation from acetone-light petroleum (b.p. 60-80°) gave 3-benzyloxy-2--ethoxycarbonyl-5-methoxyphenylacetic acid (140 mg.) as needles m.p. 143-145°. The compound had m.p. 143-145° on admixture with an authentic specimen. The infrared spectra of both samples were identical.

Attempted Resolution of 3-Benzyloxy-2-ethoxycarbonyl-5--methoxyphenylacetic Acid. - To a solution of 3-benzyloxy-2--ethoxycarbonyl-5-methoxyphenylacetic acid (1.5 g.) in methanol (30 c.c.) was added a solution of quinine (1.5 g., 10% excess) in methanol (30 c.c.). Almost immediately a white crystalline precipitate was obtained. The crystals were filtered off, washed with a small quantity of methanol and sucked dry. The salt (2.8 g.) had m.p. 194-195°. After four recrystallisations from methanol the salt was obtained as needles m.p. 195-196°, $[\alpha]_D^{CHCl_3}$ - 83° (c, 1.01)

Found: C,70.35; H,6.57%

$C_{30}H_{34}N_2O_8$ requires: C,70.03; H,6.64%.

Light absorption: λ max.2180 Å. (ε = 59,400), 2850 Å. (ε = 7,500) and 3320 Å. (ε = 5,900).

Infrared spectrum: in Nujol νmax. 1692 $cm.^{-1}$,

in chloroform νmax. 1718 $cm.^{-1}$

The salt was decomposed by dilute hydrochloric acid, and the acid extracted through ether. The acid was recrystallised repeatedly from acetone-light petroleum (b.p. 60-80°). At no stage during the recrystallisations did the acid show optical activity.

A sample of the starting material, 3-benzyloxy-2-ethoxycarbonyl-5-methoxyphenylacetic acid on repeated recrystallisation from acetone-light petroleum (b.p. 60-80°) similarly showed no optical activity at any stage of the recrystallisations.

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